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## Original Communications

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### HORMONES IN RELATION TO REPRODUCTION\*

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DEVELOPMENTS have been so enormous and rapid in the field of hormone action in relation to the reproductive system and reproductive phenomena during the last decade that to evaluate its present status is a difficult if not indeed an impossible task. Fluhmann<sup>20</sup> has cited more than two hundred references that appeared within a period of two years, dealing with the phase of ovarian-hypophyseal relationship. Conflicting findings, differences in interpretation, and lack of information will make it evident why some report of progress rather than final solutions will characterize this discussion. Rather than limit the discussion to one or two special problems with which I, personally, may have dealt, it appears more advisable on this occasion to examine the subject on a wider scale and attempt to leave with you a few general principles that appear to exist and that must be taken into consideration in deductive reasoning.

It should be emphasized that reproduction among the different vertebrate classes rests upon a basic plan more or less common to all, and that an understanding of the general problem will be aided by some comprehension of events occurring in organisms other than man. It is well appreciated that minor species differences exist in many of the separate phases, but the notion that events characteristic of other than human forms have no application to man should have been discarded long ago. An attempt will be made, therefore, to outline briefly some of the general phases of reproduction that are associated with hormone

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\*Read, by invitation, at a meeting of the Chicago Gynecological Society, April 20, 1934.

action, to present several related facts, and to offer some suggestion as to possible ways of interpreting the facts as they apply to the function of reproduction within the organism. Many of the interpretations may well be questioned, and there is no doubt that working hypotheses of the present, even though they prove useful in indicating ways and means of approaching the solution of certain of our problems, will be modified or be totally discarded as new facts and points of view are developed. It will be apparent to all that though great advances have been made in understanding the problems and mechanisms involved in the function of reproduction, a great amount is still awaiting elucidation. The suggestion of a few apparently general principles will be discussed as a basis for offering an interpretation as to the manner in which hormones may operate to control some of the events that characterize the function of reproduction.

1. The first principle to be discussed is the double functional potentiality of the sex glands. These two functions are the maturing of germ cells and production of internal secretions or hormones. It should be properly considered that each of these functions is associated with the phenomenon of reproduction rather than with general bodily health, longevity, mental processes, or religious beliefs. Maturing of germ cells is phylogenetically the older function, hormone secretion the newer.

In the simpler invertebrate forms of life, the germ cell producing function alone appears to characterize the activity of the gonads for we see little or no evidence of hormone action. In the lowest of the vertebrate types there is little hormone action, as compared with the higher types; in some of the lowest vertebrates the germ cells merely escape through the walls of the sex glands and pass to the outside without the use of specialized ducts for carrying them. But as we look at an ascending series of vertebrates, complexities are introduced by the utilization of specialized ducts to transport the sex cells to the outside, or as occurs among some members of every vertebrate group excepting the birds, there is internal insemination and retention of the developing embryo within specialized passages of the parental body. The latter are usually parts of the müllerian duct system in the female.

Characteristic of all reproductive processes is periodicity. Reproduction is not a continuously operating process but usually occurs once a year. The accessory structures, as well as the gonads themselves, come into activity only during the reproductive period. The accessory structures make possible the meeting of the germ cells at the proper place, time, and in the proper condition. It is the gonad, therefore, that matures the germ cells and makes certain that the ducts are ready to function at the proper time.

2. The second principle to be emphasized is the control of the essential accessory reproductive organs, the nonessential characteristics, and to

some extent the psychic behavior by the homologous sex hormone and the absence of an effect from the heterologous sex hormone.

The essential accessory reproductive organs include those structures that play an important or necessary rôle in reproduction. In the male these consist of such structures as the entire series of wolffian duct derivatives (epididymis, vas deferens, seminal vesicles) and the prostate and Cowper's glands, penis, etc. In the female it is the müllerian system that operates (the oviducts, uterus, and vagina) and mammary glands. Without emphasizing particularly any rigid classification of nonessential structures, they can be considered to be that miscellaneous set of characters that more or less clearly separate the sexes into dimorphic patterns but which are of no particular functional utility in reproduction as such. The horns of certain male mammals, the nuptial colorations of some lower vertebrates, the comb, wattles and specific feather patterns of birds, the voice and pubic hair distribution in man can be used as examples.

The control of these accessory reproductive organs has been abundantly demonstrated to rest upon the internal secretions of the specific or homologous sex gland. Castration entails the loss of function and involution of the male ducts and glands, which contribute the greatest part of the semen, but their function can be returned by injecting the hormone of the testicle and semen, obviously without spermatozoa, is discharged on mating. The hormonal function, therefore, appears as one of the elements in a more elaborate system than exists in lower forms. The accessory organ function provides a means of transfer of germ cells to the locality that will make possible a meeting with the germ cells of the opposite sex. In lower vertebrates including the mammals the hormones probably play a great part in stimulating the mating reactions, or sex drive, but in primates, especially in man, its rôle in this event is to be questioned to a large extent. Hormone function may be exercised continuously, as in constant breeders like rats, guinea pigs, and human individuals, or periodically as in those forms having a single breeding period during the year. In the latter, however, the period of non-function is due merely to the failure of the gonad to secrete its hormone, for injections of potent preparations can stimulate their function at any time of the year.

In the female the control is characteristically a periodic one since the oviducts, uterus, and vagina develop to a high point, recede, and develop again each five days (rat), sixteen days (guinea pig), twenty-eight days (monkey and woman) or once each year (characteristic of wild types). This control involves a preparation again for conducting the germ cells to the proper place whether this be outside the body (perhaps wrapped in protecting substances such as the jelly of amphibian eggs, or the albumin and shell of the hen's egg) or retained within it for development. The latter condition in mammals calls forth still

further specializations such as are involved in implantation, nourishing the embryo through the placenta, and finally delivering it at the proper time. In keeping with these added complexities of control more than one hormone has been elaborated. We know at least two that come from the ovary, estrin which is responsible for the growth changes and to a large extent gland activity, and the hormone of the corpus luteum which plays a large part in uterine responses in a manner that shows clearly a secondary reaction superimposed upon the actions controlled by estrin or the more primitive of the two ovarian hormones (for general references see Allen's *Sex and Internal Secretions*<sup>5</sup>).

An important consideration is the specific rôle played by these substances. The testis hormone, for example, cannot stimulate the müllerian system to its characteristic function; neither estrin nor corpus luteum stimulates the secretory function of the male accessory glands. Estrin and corpus luteum are in a sense cooperating hormones in placental mammals where resides their typical sphere of action.

A final point worthy of mention is that though these gonad hormones are quite sex specific, they are in no sense species specific. Thus testis hormone extracted from bull's testicles will grow combs on castrated cocks, repair castration damages to the accessory reproductive glands of castrated rats or in castrated guinea pigs produce semen that is discharged when proper electric stimulations are employed. Estrin from pig or human follicles serves with ease to control the female reproductive ducts of rats or chickens or induce female feathers in the cock.

3. The third principle to be emphasized is that of the threshold of effectiveness. It is too rarely appreciated that hormone storage does not occur in the body and that the response of an organ depends upon a minimal hormone level for a period sufficient for such a response to occur.

Removal of the ovaries or testicles shows clearly the absence of gonad hormone storage in the body. In female rats the vaginal smear alone shows quickly the absence of estrin and examination of the reproductive tract makes certain of its absence. Injections of estrin into ovariectomized females builds up this tract within approximately forty-eight hours and its immediate decline in the absence of injections is striking. In the male rat removal of the testis is followed by objective cytologic changes in the seminal vesicles within a period of forty-eight hours and in the prostate gland within four days. In the brown leghorn fowl estrin induces a typically colored female feather in the growing follicles but the absence of a single day's injection causes deposition of a pigment band indicative of a sub-effective concentration of the hormone.<sup>29</sup>

The gonad hormones are excreted from the body through the kidneys and the urine is now one of the most common sources for the extraction of these secretions. Whereas there is much yet to learn regarding the

relation of excretion to concentration in the body, or the possible changes in the renal threshold under varying conditions, it is apparent that a great difference exists in the excretion of these materials when injected in aqueous solutions or suspended in oil; they are readily absorbed from the aqueous solutions hence concentrations are more difficult to maintain with aqueous than with oil suspensions.

The threshold of response is an interesting phenomenon for it soon becomes apparent that a given dosage may produce a demonstrable effect upon one organ and not upon another. Thus in the rat it has been maintained that whereas a given dose of estrin will produce a typical cornified vaginal smear and uterine changes it requires many times this amount to induce the typical mating response. Among the tests for the testis hormone in mammals the most sensitive one appears to be the spermatozoon motility test, the least sensitive the electric ejaculation test, with seminal vesicle, prostate and ductus deferens responding to intermediate amounts; the low threshold to the high bears roughly the ratio of 1 to 30.<sup>45, 46, 49</sup> Benoit gives the relative sensitivity of responses to testis grafts in the cock as epididymis and vas deferens the most sensitive and passing upward in response, the comb and wattles, plumage, sexual instinct, with fighting and crowing propensities requiring the greatest amount of hormone for the control. Lillie and his students have shown that feathers on different parts of the body differed in their response to estrin: those on the breast were less sensitive to given dosages than those on the back or tail. Following low dosages, feathers on the back might be entirely female while those on the breast were not affected. This different sensitivity to hormone is correlated with the growth rate of the feathers in the different regions.<sup>29, 30, 37, 38</sup>

It becomes apparent therefore that dosage is an important phase of hormone administration, with gonad hormones as well as with thyroid hormone or insulin. A huge dose weekly does not supplant smaller daily dosages and for satisfactory effects a fairly continuous concentration must be maintained.

4. The fourth principle to receive attention is the lack of effect of gonad hormones upon the gonads themselves. It was once hoped, and still is by many, that the administration of estrin or testis hormone would stimulate the gonads. Close attention to hormone physiology, however, suggests the general principle that no endocrine gland is stimulated by products which it itself produces; the thyroid gland is not stimulated by thyroid powders or thyroxin, the pancreas by insulin, the adrenals by cortin, or the parathyroids by parathormone. There appears to be no logical assumption or demonstrated fact that would suggest that the gonads are stimulated by gonad hormones.

If one examines the observations made on the effects on the intact gonad of administration of gonad hormones those effects are injurious rather than stimulating. Thus injury to the ovary has been reported

after estrin injections into monkeys,<sup>4</sup> dogs,<sup>31</sup> and rats,<sup>36, 42, 43</sup> The general findings are reduced ovarian weights, lack of follicular activity, and atretic follicles; in normal female rats injected with estrin, ovaries have weighed approximately 45 per cent to 50 per cent of those of untreated litter mates. There are numerous reports to the effect that estrin injected into normal males produces injuries to the testes.<sup>17, 34, 48, 77</sup> Prior to 1930 this result was usually attributed to an antagonism existing between the two sexes in the general sense in which Steinach originally applied it, but when it was found that similar types of injuries followed administration of testis hormone to young males,<sup>48</sup> it became evident that another explanation than hormone antagonism was required. Testis hormone injected for periods of twenty days into normal young male rats reduced their testis weight to approximately 50 per cent to 60 per cent of litter mate control testes but stimulated the development of the seminal vesicles to a weight of approximately 400 per cent as compared with untreated controls. The explanation of this finding will appear below.

The general results of injecting gonad hormones into normal animals, therefore, is injury to the gonads (from either sex hormone) and a stimulation of the homologous accessories but not the heterologous ones. Gonads rendered defective by various means such as hypophysectomy or vitamin B deficiency and treated with homologous gonad hormones are not improved by these substances but are aided to recover by treatment with other substances.<sup>41, 50</sup> It appears that the gonad hormones have no stimulating effect upon the gonads themselves but their effects upon homologous accessories are very distinct.

5. The fifth principle to which attention is to be given is the absence in the gonads of the power of self-regulation. They are not autonomous structures endowed with the capacity of deciding when and how they should operate, but we may think of them as operating under the direction of a remote control; the seat of such control is the hypophysis.

Older clinicians had noted the association of atypical conditions in the reproductive tract with disorders in the hypophysis or pituitary gland, and the earlier attempts at hypophyseal ablation further suggested a close association between this system and the small gland attached to the lower surface of the brain. The clear demonstration of such important relationships has now been given abundantly by the striking work of Smith,<sup>69-72</sup> Smith and Engle,<sup>73</sup> Zondek,<sup>81, 82</sup> and Zondek and Aschheim,<sup>83, 84</sup> and by others.

In general it has been shown that successful removal of the pituitary gland entails a severe degeneration of the gonads in either sex. Testes and ovaries become inactive and produce neither germ cells nor internal secretions or hormones, and due to the absence of the hormones the entire reproductive tract undergoes involution essentially as severe as after castration. The introduction of fresh pituitary gland substance im-

mediately after hypophysectomy prevents such a severe inactivation of the entire system, or if the typical changes have been permitted to develop, the fresh gland substance causes the system to be repaired to the normal state structurally and functionally. Furthermore, it was found by Smith and Engle and Zondek and Aschheim that the introduction of fresh pituitary gland substance subcutaneously into very young rats led to a precocious development of the entire reproductive system; this effect is somewhat more pronounced in females than in males. The ovaries increased tremendously in size; many more ovulations occurred in animals before weaning than would ever occur at one time in the normal adult; and the uterine development was quite characteristic of the mature animal.

It has furthermore been shown that substances contained in the urine of pregnant women, likewise, exert a marked stimulating effect upon the ovaries, but in a manner somewhat different from fresh pituitary substance. It is this stimulating reaction that constitutes the basis for the Zondek-Aschheim pregnancy test. Substances that stimulate the gonads have been derived from several sources, such as fresh and dried pituitary material, the placenta, urine or blood of pregnant women, but it is not to be suggested that these materials from different sources are identical. Neither is there conclusive evidence to show that the ultimate source of these materials is the hypophysis. Indeed there are many elements suggesting its origin elsewhere particularly in the decidua or certain types of epithelial growths (chorionepithelioma).

It is to be remembered, therefore, that both functions of the gonad (germ cell production or hormone secretion) depend upon a stimulation from the pituitary gland and that many gradations in gonadal activity can be produced in the amount of stimulating substances present. Zondek has referred to the pituitary as the "motor" for the gonads.

6. The next principle to be emphasized is that hypophyseal activity is modified by the gonad hormones; there is a reciprocal interaction between the gonads and the pituitary. The modification may be expressed as an inhibition, or a suppression, of hypophyseal activity of such a nature that pituitary secretions are delivered into the blood stream in reduced amounts.

The capacity of the pituitary to stimulate the gonads does not remain constant but varies, at least in some forms, in association with the amount of gonadal secretions present in the body. Thus Engle<sup>15</sup> and Evans and Simpson<sup>16</sup> determined that the hypophysis of castrated male or female rats was more potent in its stimulating effect after transplantation into the immature organism than was that taken from normal animals of equivalent age. A similar situation has been demonstrated for the rabbit by Smith, Severinghaus, and Leonard<sup>16</sup> and for the guinea pig by Severinghaus.<sup>17</sup> Thus the presence of a functional gonad is associated with a lowered capacity of the hypophysis to exert its stimu-



lating powers. In ovariectomized women, and some in the menopause, Fluhmann<sup>18, 19</sup> was able to demonstrate the presence of a gonadal-stimulating substance in the blood stream (presumably from the hypophysis) which he was not able to demonstrate in normal women. Hamburger<sup>21</sup> finds gonadal-stimulating substances in the urine of both castrated men and women two months to fifteen years after operation that are different from the pregnancy urine derivatives.

The influence of the gonad hormones in lowering the capacity of the hypophysis to stimulate the gonads has also been demonstrated by injecting normal or gonadectomized animals with these substances, or by causing the intact gonad to secrete a larger amount of hormone than is normal. Meyer, Leonard, Hisaw and Martin<sup>36, 42, 43</sup> injected normal female rats with estrin and determined that their hypophyses were decidedly less effective as stimulating agents than those removed from untreated litter mate females. Furthermore, castrate hypophyses though ordinarily possessing greater stimulating power than normal ones do not show more activating powers if the castrate animal has been treated with estrin. Instead of injecting the gonad hormones so as to increase their concentration in the animal body, one can cause the intact gonad to secrete greater quantities if the animal is treated with gonadal-stimulating agents, such as prolan (a urine derivative). Thus the hypophyses of such animals are subjected to the effects of greater than normal concentrations of gonad hormones. Kuschinsky<sup>33</sup> and Leonard<sup>35</sup> have found that hypophyses from normal male and female rats treated with prolan are less effective than those from untreated animals. That this lowered capacity is due to the excess gonad hormone arising from the stimulating action of prolan on the gonad and not from the action of prolan on the hypophysis is indicated by the fact that injections of prolan into the gonadless animal does not reduce the stimulating capacity of the pituitary when this is compared with castrates not so treated.

In still another manner the variation of the stimulating capacity of the pituitary associated with gonad-hormone concentrations is indicated. Smith and Engle<sup>74</sup> found the hypophysis of female guinea pigs at estrum to have less gonadal-stimulating capacity than those during diestrus. Estrum marks the climax of the estrus cycle and is the end of a period in which the female hormones have been present in amounts sufficient to bring on the changes characteristically associated with mating. A low activity of the hypophysis at this time gives some basis for assuming that the depression was brought about by the presence of the gonad hormones whereas in the diestrus phase it is evident that estrin effects are low and probably corpus luteum secretions as well. Excretion or destruction of the gonad hormones therefore can be supposed to release the inhibitory effects on the hypophysis, and it would again come into activity. Wolfe<sup>79, 80</sup> likewise found in the sow a variability

in hypophysis activity during the cycle of the general nature that hypophyses from animals whose ovary contained small follicles up to 6 or 8 mm. in diameter would produce ovulation in rabbits in doses of 1 mg.; hypophyses from animals possessing follicles of 10 mm. diameter required 20 mg.; hypophyses from animals possessing active corpora lutea in the ovaries produced consistent ovulation-inducing stimulation in doses of 40 mg. Thus hypophyses from animals with a progressively increasing gonad hormone content were less and less efficient in their gonadal-stimulating capacity. Freshly developed corpora lutea have been shown by several investigators to contain estrin as well as the corpus luteum hormone. There are many suggestions that corpus luteum hormone, as well as estrin, acts to suppress the hypophysis but to my knowledge the direct evidence has not been presented to show that estrin-free corpus luteum hormone does inhibit the hypophysis. Since the indirect evidence for this is strong it is assumed to be the case for the purposes of this discussion.

If the idea presented above is carried to the state of pregnancy, it should follow that the hypophyses of pregnancy would exhibit a lowered capacity for gonadal stimulation than normal animals. It is during pregnancy that the greatest amounts of gonadal-stimulating substances appear in the urine and to some this has indicated that the hypophysis is more active, not less active. However, since there is no convincing evidence that these substances are actually hypophyseal secretions and since there are many lines of indirect evidence that they are produced not in the hypophysis but in the decidua, more convincing evidence should perhaps be obtained from the effects of transplanting the hypophysis of pregnancy. This has been done in several instances. Bacon<sup>6</sup> found the stimulating power of the hypophysis of pregnancy in the cow to be lower than in the normal animal, and Philipp<sup>60</sup> has found a decidedly less stimulating capacity in the hypophysis from pregnant women. Wolfe<sup>80</sup> used the rabbit ovulating dose of hypophysis and was inclined to believe that the pregnancy hypophysis contained a lower stimulating potency than those from normal animals; his results were not entirely consistent when hypophyses were removed at different stages of pregnancy. Evans and Simpson,<sup>16</sup> however, reported but little difference in the stimulating effect between hypophyses of pregnancy in cows and rats and normal ones.

There appears to be little doubt, therefore, that the gonad hormones do suppress the activity of the hypophysis, and since the evidence indicates that these hormones are without direct effect on the gonads, Moore and Price<sup>48</sup> have interpreted the deleterious effects of gonad hormones on the gonads themselves as being an indirect effect induced by suppression of the hypophyseal secretions that are necessary to maintain the gonads in a functional state. When the gonad hormones which cause gonadal injury are accompanied by some gonadal-stimulat-

ing agent that, temporarily at least, can act for the hypophyseal secretions, then the gonad hormones are not injurious to the gonads.

Since emphasis has been placed upon some of the principles of hormone actions and interactions, it may be of interest to consider some of the possible mechanisms in the actual control of a few of the phenomena characteristic of reproduction. That we do not have sufficient information at the present time to enable us to adequately explain the control of the characteristically rhythmic processes in reproduction cannot be doubted. However, some profit may accrue, at least in suggestions as to ways to consider the various events, in constructing working hypotheses looking to some explanation of the basic phenomena associated with this function.

Certain observations from our laboratory necessitated an explanation along different lines than those current at the time, and a working hypothesis based upon the fundamentals discussed above was attempted. Since many observations from other laboratories appeared also to fit into the conception, it was extended to include a suggested interpretation for other than our own experiments.<sup>44, 47, 48, 51, 55, 68</sup> Stress is laid upon the reciprocal influence between the hypophysis and the gonads as a mechanism for the control of several different events, and I should like to dwell upon this suggested mechanism in considering the control of estrus cycles, of lactation, and of menstruation.

#### CONTROL OF BREEDING CYCLES

The breeding cycles of vertebrates, generally speaking, occur once a year, most conspicuous exceptions occurring in birds and mammals, though there are a few special exceptions outside of these two groups. In birds and mammals the majority of species still exhibit the annual cycles, and the spring months are the usual ones for reproductive activity. Among the mammals the yearly cycle is perhaps still the usual one, but the range of cyclic activity is from recurring periods of five days for the rat and mouse, to sixteen days for the guinea pig, and thirty days for the primates, man and monkeys, to the annual period for the wild types. These cycles, ordinarily termed estrus cycles, have as their essential features the increase in size of the uterus, the growth and ripening of follicles in the ovary and the development of a psychic state in the female such that she will mate with a male. The general law of nature, transgressed by the primates, is mating for reproductive purposes only; that is, mating occurs at a point in the cycle best for the meeting of the germ cells.

An attempt has been made to explain the exacting control of these periodic events on the basis of the reciprocal influence between the ovary and hypophysis;<sup>44, 48</sup> at almost the same time and entirely independently a somewhat similar hypothesis was suggested by Brouha and Simonnet.<sup>12</sup> As an example, let us start with a quiescent ovary in the rat. The hypophyseal secretions stimulate the ovary to follic-

ular development and the secretion of estrin. The follicles mature and ovulation occurs. Meanwhile estrin stimulates the reproductive tract and the climax of the cycle occurs with mating. The presence of a high estrin content is necessary to accomplish these changes but as this substance is increased in the organism the hypophysis is so influenced that it delivers an insufficient quantity of its secretions, hence the ovary does not immediately mature a new group of follicles but becomes for a time relatively inactive. When the estrin content is reduced through excretion or possible destruction, the inhibition is removed from the hypophysis, and it again resumes its activity and a new cycle is initiated. The corpus luteum in the rat probably does not play a part in this cyclic control (or if it does a relatively brief one), for it has been demonstrated that the deciduomata reaction of Loeb (a test for corpus luteum hormone) cannot be demonstrated in the rat except by producing a pseudopregnant state; this is accomplished by sterile matings or by mechanical cervical stimulation.<sup>39</sup>

In the somewhat longer cycle of the guinea pig, and that of primates, the corpus luteum probably does play a part. The active corpus luteum phase is longer than in the rat and this fact probably offers an explanation for the longer cycles. Removal of the corpus luteum was long ago shown by Loeb to result in an immediate new cycle and by this means the cycles of the guinea pig can be greatly reduced in length; injections of corpus luteum extracts on the other hand lengthen them.<sup>57</sup> That the long period of ovarian inactivity is due to an insufficient ovarian stimulation, usually provided by the pituitary, is shown by the fact that the ovarian cycle is renewed, even during pregnancy, by the introduction of gonadal-stimulating agents.<sup>58, 80</sup>

The primate cycle has been somewhat modified but is believed to operate similarly. Estrum, or a distinct acceptance period associated with ovulation time, no longer exists but the ovulation cycle is present and the phenomenon of menstruation has been introduced at a midpoint between two ovulation cycles.

A slightly different situation prevails in the estrus cycles of the annual variety. Investigations in this laboratory<sup>51</sup> on the ground squirrel (*Citellus tridecemlineatus*) found abundantly in the Chicago region show that the ovary is essentially inactive for almost ten months of the year. It can be thrown into activity at any time of the year by the introduction of gonadal stimulants, hence its inactivity is due to an absence of the hypophyseal stimulant. Mr. Simmons has determined that the hypophysis of these forms is inactive during the period of ovarian quiescence but possesses stimulating capacity at the time of the year when ovarian activity is present; stimulating capacity was determined by implantation of the hypophyses into immature female rats.

In these annual breeding types, therefore, hypophyseal inactivity is prolonged instead of temporary as in constant breeding types, and it is recognized that environmental factors play a part in its periodicity. It is assumed that this additional factor from the environment need not be the same for all species. Such environmental agents are not entirely hypothetical, however, and some advancement has been made in acquiring an understanding of them but so far it is only a beginning. Thus Rowan<sup>62, 63</sup> trapped small migratory birds (*Junco*) on their southward flight from the Alberta region of Canada and confined them in open cages over winter. Lengthening the daily period of light by the use of electric light for ten minutes each day beginning in September and October, in an attempt to duplicate the progressively increasing lengths of spring days, resulted in a stimulation of sexual activity. Despite the external environmental temperatures of from 20 to 40° below zero the testes of these birds increased in weight by hundreds of times and spermatozoa were produced in midwinter. Progressive shortening of the daylight periods led to recessions in this activity and the cycles could be controlled at will. Bissonnette<sup>9, 19</sup> confirmed similar responses to increasing light in the introduced European starling (*Sturnus vulgaris*).

The stickleback fish (*Gasterosteus aculeatus*) breeds once a year and develops a characteristic nuptial dress during this period. Craig-Bennett, however, was able to induce these changes at will during different seasons in the year by changing the temperature of its habitat. Light manipulations failed to show any influence and the changes were accomplished as well in total darkness by the temperature changes in the light.<sup>14</sup> In one annual breeding mammal (ferret) Bissonnette<sup>11</sup> was able to induce estrus and mating outside of the regular season by progressive increases of the daylight period, and Hill and Parkes<sup>26</sup> obtained evidence that the stimulation in this form operated through the hypophysis. Baker and Ranson<sup>7</sup> modified the breeding of field mice to a marked extent by light.

Thus it is beginning to be recognized that certain environmental agents operate in some manner to influence the hormone activity of the organism; in annual breeding forms this added environmental factor operates upon the controlling mechanism that exists in those forms that are not similarly affected by their environment. In the ground squirrel the environmental factor, or factors, which are operative do not appear to be light. It is not yet entirely clear whether the environmental factor merely operates to stimulate the activity of the hypophysis or operates to remove some analyzable inhibition. The difference may finally prove to be that hypophyses in such annual types do not regain their full activity after the hormonal inhibition is removed, or it may be that a prolonged hormonal inhibition remains until it is released in some manner by the operating environmental agent.

The control of breeding cycles can thus be understood by the application of some of the general principles of hormone action discussed above but that many changes in the hypothesis will be required as our knowledge increases is not to be doubted. The activities of the males can also be understood on the basis of this working hypothesis when the fundamental facts are considered. This has been developed in a paper published elsewhere (Moore<sup>52</sup>).

#### CONTROL OF MAMMARY GLANDS

Can this working conception of reciprocal influences of hormones give us any suggestion in regard to the mechanisms operating in the control of growth and function of the mammary glands? It has proved to offer suggestions for experimental work in this laboratory and some of the findings have been interpreted on such a basis. It must be kept in mind that in this phase of reproductive activity there are many species differences but that fundamentally the same concept appears not unreasonable.

Smelser<sup>68</sup> has given a clear demonstration that the mammary glands of castrated male and female guinea pigs respond with equal developmental intensity to the same dosage of estrin injected subcutaneously. The absence of mammary growth in males, therefore, is clearly understandable on the basis of an insufficient amount of estrin to stimulate their development rather than to any inability of these rudimentary structures to respond; equipotentiality of the mammae appears to exist in

the two sexes. A second point is that ovarian grafts in either gonadectomized sex, stimulate mammary growth to a state equal to or greater than that in normal pregnant females, but such hypertrophied mammae do not lactate as long as a functional ovarian graft remains. The peculiarity exists that ovarian grafts in castrated males lead to greater development of the mammary glands than similar grafts in females. Thus in a brother-sister pair of guinea pigs a few days after birth removal of the sex glands of each but with the implantation of one of the ovaries into the male kidney and the other into the female kidney (autograft), the mammary glands of the male always grow larger than those in the female. The explanation of this unexpected result is merely that the ovarian graft in the male secretes a greater amount of estrin due to a greater potency of the male pituitary to stimulate gonadal activity than the female pituitary. This has been shown to hold in another relation by Severinghaus.<sup>67</sup> It is possible that an added factor is introduced in the findings of several investigators that the male hypophysis is less easily modified by gonad hormones than is the female.<sup>28, 54</sup>

Growth and lactation, however, are two different phenomena; since mammary glands induced by estrin injections or by ovarian grafts, or the large mammary glands of pregnancy, do not ordinarily lactate until another stimulus is added.

Stricker and Grüter<sup>78</sup> demonstrated that the injection of pituitary gland substance into rabbits had a lactation-stimulating effect; following a pseudopregnant state the anterior pituitary treatment induced lactation whether the ovaries were present or had been removed. In this laboratory mammary glands were developed in gonadectomized male or female guinea pigs which lactated within forty-eight to sixty hours after pituitary treatment.<sup>55, 56, 68</sup> Riddle, Bates and Dykshorn<sup>61</sup> believe the lactation-stimulating substance of the pituitary is a hormone that differs from the growth or gonadal stimulating hormone. They have named the hormone "prolactin" and it has been reported to have pronounced beneficial effects clinically.<sup>32</sup>

These, and many other findings not mentioned here, emphasize a mechanism in which estrin stimulates the gland to a high state of development and pituitary hormones induce it to lactate. Despite the fact that in the guinea pig lactation can be induced in the male mammary glands under conditions which preclude any effect of the corpus luteum hormone still this in no way proves that corpus luteum fails to play a part even in this species in normal lactation. In some mammals it seems to be well established that the corpus luteum hormone does enter into the chain of events by an effect upon the mammary gland that is superimposed on estrin stimulation. Corpus luteum hormone alone does not influence the mammary growth or secretion. Estrin alone stimulates their growth but in some species this is carried still further by corpus luteum hormone; as long as these hormones predominate, however, lactation does not occur.

Upon the basis of observation and experiment we could suggest the controlling mechanism upon somewhat the same basis as that suggested as operating in the control of the estrus cycles. Thus growth occurs under the influence of estrin and during pregnancy the corpus luteum hormones operate to complete the full development of lobules. At delivery the recession of the corpus luteum and the casting off of the decidua remove the gonad hormones that have suppressed the pituitary gland, and, with the inhibition removed, the pituitary becomes active again and stimulates the mammary gland to lactate. The fact that many animals experience an ovulation immediately after delivery is evidence that the pituitary activity is renewed. The following notations on actual observations of Nelson and Smelser<sup>55, 56, 68</sup> give some

of the bases of fact that suggest this type of control: (1) male or female guinea pig mammary glands stimulated to growth by estrin do not secrete while injections continue. They will lactate, however, (a) if pituitary extracts are administered to stimulate secretion or (b) if estrin injections are discontinued and the animal's own pituitary can come into activity. (2) Ovarian grafts in gonadectomized males or females produce large glands that do not lactate. They will lactate (a) if pituitary substance is given or (b) if the graft is removed and the animal's own pituitary can resume activity. (3) Removal of the ovaries of a pregnant guinea pig may produce abortion but in some cases it does not. If abortion occurs lactation follows; if abortion does not occur lactation does not occur until delivery; after this event all sources of hypophyseal-suppressing gonad hormones are removed (ovary and decidua) and lactation follows. Removal of the ovary and fetus, with retention of decidua, is not followed by lactation but upon removal of the decidua lactation follows. (4) Lactation occurs normally following parturition but it fails to occur if estrin injections are given immediately after delivery. The pituitary that should have become active after delivery was apparently prevented from resuming activity by the injected estrin. Finally, lactation following parturition is prevented by hypophysectomy.<sup>59, 65, 66</sup>

It is to be seen that the reciprocal influence between the ovary and pituitary is suggestive as a means of visualizing a mechanism that may operate in the control of mammary gland activity.

#### THE CONTROL OF MENSTRUATION

It may be of interest to carry the speculations still a little farther and inquire whether this working hypothesis holds any suggestions for visualizing the control of menstruation.

The notion has long been current that ovulation and corpus luteum formation were indispensable precursors of uterine bleeding. That notion has now been dispelled as an absolute requirement for external bleeding from the uterus at normal menstruation intervals. The work of Corner<sup>13</sup> and Hartmann,<sup>22, 23, 24</sup> on monkeys presents an abundant amount of evidence that ovulation or the corpus luteum are not required, and Bartleman<sup>28</sup> has obtained strongly suggestive evidence that a similar condition can be present in the woman.

If we look at the experimental conditions under which uterine bleeding has been induced we find that estrin injection into monkeys leads to growth and development of the uterus, though it does not attain the complete premenstrual stage; it does so, however, if the corpus luteum hormone effect is added to the estrin stimulation.<sup>27</sup> As long as the injection of these hormones continue, bleeding does not occur, but when they cease, bleeding follows.<sup>1, 2, 3, 40, 53</sup> Pituitary substance injected into monkeys with intact ovaries stimulates the ovary to secrete estrin and may cause luteinization but usually external bleeding does not occur as long as the pituitary injections are carried on. When these are stopped, however, external bleeding occurs within a few days.<sup>64</sup> We may see in this the possible recovery of a pituitary to secrete its hormone after the estrin inhibition is removed and acting upon a sensitized uterus, bleeding occurs. Hartman and his colleagues<sup>25</sup> have emphasized more than others the probable rôle of the pituitary in menstrual bleeding and have suggested the possibility of a specific bleeding hormone, but Saiki<sup>64</sup> failed to find it necessary to postulate such a separate hormone. The latter investigator found also that whereas external bleeding was assured after discontinuing pituitary treatment of normal monkeys, bleeding was prevented by the injection of estrin;

when these estrin injections were stopped, bleeding occurred. Smith and Engle<sup>75</sup> similarly induced conditions that were certain of producing bleeding (by gonadal stimulants first, succeeded by ovariectomy), but the bleeding was prevented for periods up to twenty-eight days by injecting corpus luteum extracts having only a trace of estrin. There are many lines of evidence suggesting that the hormone of the corpus luteum exerts a depressing action upon the hypophysis, and it is possible that the control of these experimental types of bleeding will find their explanation upon this reciprocal interrelationship between the gonads and the hypophysis.

Sufficient detail has been presented to indicate that many of the phenomena of reproduction are interpretable upon the basis of the working hypothesis presented. This type of explanation has been of service in this laboratory in suggesting lines of experimental attack upon several problems. It is anticipated, however, that many other factors will be found to enter into the mechanisms of control of the phenomena discussed, and it may be admitted that several facts are difficult to fit into the suggested scheme. With an increase of our knowledge and the evaluation of factual information, there is little doubt that our understanding of the mechanisms of control will advance. It is probable that other endocrine glands will have to be placed in the chain of events as a necessary link, but until the interpretations are clear working hypotheses will have a place.

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#### DISCUSSION IN ABSTRACT

PROFESSOR ANDREW CONWAY IVY.—Dr. Moore has made it easier to teach the interrelation between the gonads and the anterior lobe by enumerating the principles of this interrelationship.

In reference to the effect of environmental factors on the functioning of the anterior lobe and gonads, i.e., the effect of light and temperature, it would appear that in these and other instances we have evidence suggesting that the function of the anterior lobe may be affected by factors operating through the nervous system.

I should like to ask whether the atrophy of the testicle which follows the injection of the male sex hormone is due to a direct effect of the male sex hormone on the testicle or to a suppression of the hypophysis by the male sex hormone?

A second question: Is there any recent experimental evidence indicating that the adrenal cortex may be concerned directly with premature development of the gonads? I ask this question, having in mind the fact that adrenal cortical tumors are associated with certain changes attributable only to the gonads. Has anyone shown that the adrenal cortex affects the hypophysis in such a manner as to account for the gonadal changes?

The third question pertains to progesterin as related to the paper Dr. Browne has presented. Up until about a year ago there was no direct evidence showing that

progesterin is actually formed by the human corpus luteum. I should like to know if there is any recent evidence. That question is intimately related to the clinical use of prolan B or the luteinizing hormone of pregnancy urine, or even of a preparation of progesterin made from lower animals.

Before the treatment of essential dysmenorrhea with "hormone preparations" can be placed on a true scientific basis, two types of experiments must be performed in women suffering from essential dysmenorrhea. First, it must be shown by analysis of the blood or urine either that an excessive quantity of estrin is being produced, thus rendering the uterus more irritable, or that there is a retention of estrin in the body due to a decrease in formation of progesterin which would also render the uterus more irritable and also according to the work of Smith and Smith, cause retention of estrin in the blood because progesterin increases the elimination of estrin in the urine. Second, it must be ascertained if for some reason, either developmental, hormonal or psychic, the musculature of the uterus in the patient is more irritable or sensitive than normal, or the endometrium is abnormal histologically. When such dysfunctions are demonstrated or when the patients are selected on a known etiologic basis and relief from dysmenorrhea is obtained by injection of the hormone indicated for the etiologic condition, then one has adequate reason to state that the relief was not due to psychotherapy but to a true direct response.

Experimental work on animals illuminates the way and provides the indications for what should be tried and expected in the human being.

DR. LEON KROHN.—For several months my associates and I have been treating functional dysmenorrhea with a carefully prepared and standardized preparation of progesterin. Our method of approach differs from that of Dr. Browne in that he is attempting to stimulate the production of progesterin by using follutein whereas our therapy is substitutional. The experimental work of Novak and Reynolds, Hisaw, Morrell and others suggests the rationale of this procedure.

Dr. Ivy mentioned that in order to justify this form of treatment, one must first demonstrate an abnormally high estrin content in the blood just before the onset of menstruation, in patients suffering with this type of dysmenorrhea. Instead of doing this, we are obtaining a small piece of endometrium a few days prior to the onset of menstruation in an attempt to demonstrate a proliferative type of endometrium instead of the normally present secretory phase. We are also using progesterin in the treatment of threatened and habitual abortion.

Although we have not treated a sufficiently large group of cases over a long enough period of time to draw any definite conclusions, the results thus far obtained are very encouraging.

PROFESSOR MOORE (closing).—The contention that gonad hormones are not gonadal stimulants is based upon two lines of evidence: (1) that injection of the gonad hormones in normal animals, or even in cases of experimental gonadal interference, has failed to give evidence of stimulation either from estrin on the ovary or from testis extracts on the testicle. (2) Contrary evidence is available from the fact that actual gonadal injury in both sexes follows injection of gonad hormones into normal animals. The injurious effects noted have been interpreted as indirect effects in which the gonad hormones so act upon the hypophysis as to lower the output of its gonadal-stimulating, or -maintaining, hormone to such an extent there is an insufficient amount of hypophyseal secretions to maintain the gonads in a healthy, active condition. The effect is not believed to be a direct one upon the gonad itself but upon the hypophysis which controls the gonad.

The general scheme of such an interaction as I have indicated for the hypophysis and gonads raises the question of the cooperation of other endocrine products as

mechanisms of control. Time permits the barest suggestion of other conditions that appear to need a new point of view. The notion that exophthalmic goiter is conditioned by a diseased thyroid gland, indicating removal of the organ, may need more mature consideration. Experiments have shown that injections of hypophyseal extracts produce exophthalmos in guinea pigs, either in the presence or absence of its thyroid gland; and that thyroid hyperplasia can be induced by pituitary extract administration. Should we, therefore, question whether the thyroid secretions of a disordered gland are the causative agents or whether the condition of the gland as well as the eye protrusion may not be merely two separate expressions of the same underlying disordered function located elsewhere than in the thyroid gland itself. Sexual precocity may be largely abolished by removal of the sex glands, but these may not be at all the seat of the disorder; they are merely responding to a disordered function located elsewhere. Sufficient knowledge of the biology underlying them may perhaps change radically the present methods of approach in treatment.

We cannot yet, I think, adequately place the adrenals in their possible cooperative position in regard to reproduction. Such findings as precocious sexual maturity associated with hypernephromas and the normal restoration upon removal of the tumor give us the available evidence of interrelationships. One group of workers affirms, and another denies, that cortical hormone administration induces precocious sexual maturity.

The pineal influence is equally intangible. Some pineal tumors have been associated with certain sexual disorders but another similar tumor may not be so associated. Experiments on pineal implants have been disappointing in offering suggestions as to its effect.

I believe Dr. Ivy's remarks regarding the rôle of corpus luteum hormone in quieting uterine motility as an explanation of effects in cases of dysmenorrhea are well taken. The work of Reynolds and Novak makes it appear probable that they are working along correct lines.

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Halbrecht, B.: Recurrence of Fetal Malformations, *Bull. de la Soc. d'obst et de gynec.*, p. 99, January, 1934.

The author reports two cases where fetal monsters were born twice to the same mother. In the first case, both babies had hydrocephalus. The second patient first gave birth to a hydrocephalic child and in a subsequent pregnancy she bore an anencephalic monster.

In both cases the Wassermann reaction was negative. In the other cases of fetal monsters which the author has seen during the past ten years the incidence of positive Wassermann reactions was no greater than among the rest of the obstetric patients. This is not astonishing according to the author because we cannot rely upon the Wassermann test in cases of hereditary syphilis. He believes that fetal malformations most likely represent hereditary syphilis in the second and third generation. Noteworthy is the fact that at autopsy there is no evidence of syphilis. In spite of this, the author believes that such cases should be treated specifically for syphilis.

J. P. GREENHILL.

## THE FETAL MORTALITY IN DIFFERENT TYPES OF TOXEMIA\*

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THIS study is a review of 1,500 cases from the records of the Sloane Hospital for Women. Only 1,156 cases are reported, however, for some were deemed either not toxic, or the work-up in the earlier cases was insufficient to establish a definite diagnosis. The study includes the cases since the unit system went into effect in 1922. All the charts signed out as *toxemia* were used; cases of pernicious vomiting were omitted.

Among the 1,156 cases, 120 patients had pregnancy terminated early, either by dilatation and curettage or by hysterotomy. There are, therefore, 1,036 cases which are included in the principal portion of the paper.

For an analysis of this type to be of value, it is essential to have definite clinical criteria for the classification of the cases. Every author, medical school, and hospital has its own classification of toxemia. These classifications are as varied as the theories of the etiology of the convulsive state associated with pregnancy. Time alone will reveal which may be correct. The name of an illness should be such that the trained physician will immediately associate it with a definite symptom group and a definite clinical course. This should not be variable and should be the same regardless of location or school.

For this reason each type of toxemia whose fetal prognosis is under discussion is described, and each case is pigeon-holed according to symptoms, laboratory findings, and clinical course, and *not* according to terminology. Regardless of classification, these cases may be recognized everywhere and a statistical prognosis made.

### HYPERTENSIVE GROUPS

Because hypertension is its outstanding feature, the largest group of the series, 585 (56.5 per cent) is named the hypertensive group and it is divided into three subdivisions: mild, moderate, and severe.

*Mild Hypertension.*—The mild cases that fall into this group have systolic blood pressure readings of 130 to 150, and diastolic readings of 90 to 110. These cases may present no disturbance other than an elevated blood pressure. The elevation may begin at any time during pregnancy but generally in the later months. It may be present for two, three, or more determinations. Postpartum it returns to normal.

\*Read at a meeting of the New York Obstetrical Society, May 8, 1934.

In future pregnancies it is likely to reappear but this is not absolute. If it should then be present, it may be of the same level or, more frequently, it is a little higher. These patients feel perfectly well and have no complaints. Occasionally they may develop slight edema of ankles or hands or of both. The urine examination is negative, although occasionally a very faint trace of albumin may be found. The blood chemistry and renal function tests are normal. The eyegrounds may be normal or there may be the early vessel changes of spasticity.

TABLE I. THE FETAL MORTALITY IN PREGNANCY TOXEMIA

TYPE OF TOXEMIA	NUMBER OF CASES	FETAL DEATHS DUE TO TOXEMIA	MORTALITY PERCENTAGE
Hypertension			
Mild	338	11	3.0
Moderate	197	7	3.6
Severe	50	15	30.0
With late albuminuria	27	9	33.3
Nephritis			
Mild	121	19	15.7
Moderate	130	41	31.5
Severe	71	49	69.0
Preeclampsia	29	7	24.1
Eclampsia	63	26	41.2
Nephritis or preeclampsia	10	4	40.0

The group comprises 338 cases. The total number of dead babies in the group was 19 (5.6 per cent); but among the 19, two babies were congenitally syphilitic, three were born to mothers with placenta previa, one had a congenital deformity, one was a breech delivery, and one had a tight knot in the cord. That leaves eleven babies which died presumably as the result of toxemia. Two were stillborn full-term, five stillborn macerated, two were born alive and died fourteen days after birth, one premature died, and one patient aborted. The corrected deaths are 11 or 3 per cent.

*Moderate Hypertension.*—The blood pressure of the group of moderate hypertension ranges from 150 to 180 systolic and 90 to 110 diastolic. The condition may arise in a first pregnancy, but it more frequently occurs in a patient who has had mild hypertension in a previous pregnancy. The time of occurrence in pregnancy varies from the end of the first trimester to the sixth or seventh month. Once the blood pressure level has been reached it is usually maintained even in spite of treatment. After delivery the hypertension disappears, to reappear at a variable later date and, then, usually in lesser degree. The symptoms in pregnancy again are, as a rule, nil, although headaches, "spots before the eyes," and slight edema may be present. The urine is free from albumin. The blood chemistry and renal function tests are normal. The retina may be normal or may show variability of vessel contour. These patients, in spite of their hypertension, surprise us very often by their appearance of well-being.

The cases totalled 197 or 19 per cent of the entire series. The dead babies numbered 14 (7.1 per cent); but if we exclude syphilis three, fibroids one, congenital deformity one, congenital pulmonary edema one, pyelitis one, the corrected number is 7 (3.6 per cent).

*Severe Hypertension.*—A blood pressure reading of 180 to 280 systolic and 110 to 170 diastolic during a pregnancy is a source of apprehension to the attending physician. The course of the hypertension in this group differs from that of the others. Most of the patients are known hypertensives, and pregnancy is an incident. As gesta-

tion advances the blood pressure rises until when term is reached the terrifying hypertension results. These cases occur almost entirely in multiparas and one of the reasons they are not more numerous is that pregnancy is frequently terminated prophylactically. Postpartum the blood pressure comes down slightly but generally remains elevated far in excess of what it was at the beginning of the pregnancy. Symptoms directly due to the marked hypertension are usual. Edema is frequent, albuminuria is absent. The retina shows spasticity of the vessels, occasional patchy edema, and, commonly, one or two hemorrhages. Blood chemistry is not characteristic and may show either high normal figures or a slightly elevated nonprotein nitrogen and urea.

This series contains 50 cases (4.8 per cent). The dead babies number 16 (32 per cent); and if one syphilitic case is subtracted the corrected number of babies whose death is due solely to toxemia is 15 (30 per cent).

*Severe Hypertension With Albuminuria.*—Closely related to the severe hypertension group, and merging with the most severe of the next general group to be described, is a series of 27 cases (2.6 per cent of total series) which has been classified as severe hypertension showing late albuminuria. These patients run an elevated blood pressure for months. The urine gradually shows increasing albuminuria in the seventh and eighth month of gestation. Postpartum the blood pressure subsides somewhat but does not approach normal. The albuminuria persists for months. The blood chemistry taken within one to three days postpartum will show a very slight nitrogen retention. The retina shows the same changes as the severe grade of hypertension cases. Symptoms are also similar. Edema is usual and may become marked.

Nine babies (33 $\frac{1}{3}$  per cent) died as the result of the toxemia.

#### NEPHRITIC GROUP

The second large group, 322 cases (31 per cent), is the nephritic group which in turn is divided into mild, moderate, and severe varieties. This group is characterized by albuminuria and varying degrees of hypertension.

*Mild Nephritis.*—The criteria for the identification of the cases of mild nephritis were the following: (a) blood pressure readings 130 to 150 systolic, 80 to 100 diastolic, together with a persistent albuminuria, noted as Heavy Trace Albumin; (b) normal blood pressure with albuminuria from heavy trace to 5 per cent. Blood chemistry is normal. The eyegrounds occasionally show patchy edema. Postpartum the hypertension disappears in a day or two and albuminuria clears in a few weeks to a few months. These patients are almost entirely symptom-free except for edema. Almost all show varying grades of ankle and hand edema.

The mild type includes 121 cases (11.5 per cent), and in these there were 20 dead babies (16.5 per cent); excluding one fetal death due to congenital abnormality, the deaths due to toxemia were 19 (15.7 per cent).

*Moderate Nephritis.*—The symptoms of the moderate nephritic group may start insidiously or most acutely. The blood pressure gradually rises and, coincidentally, or more often a little later, albuminuria appears. As term approaches both hypertension and albuminuria become more marked. Symptoms that go with a corresponding mercury level appear. Edema, oliguria, and visual disturbances are common. Exposure to cold or rain may precipitate an acute onset, or such may occur without any apparent reason. In the beginning this type cannot be distinguished from the acute preeclamptic type of toxemia. The occurrence in multiparas, previous history of toxemia, presence of nitrogen retention, and the course of the disease serve to make the differential diagnosis. After a few days' bed rest and sedatives the patient quiets down and the true nature of the illness may be recognized. Postpartum

the hypertension and albuminuria persist and may not subside for many months or even years. The following types are included in this group: (a) blood pressure ranging from 150 to 180 systolic, 90 to 110 diastolic and albuminuria heavy trace to 5 per cent; (b) blood pressure 130 to 150 systolic, 80 to 110 diastolic and albuminuria from 5 to 15 per cent; (c) normal blood pressure and albuminuria 5 to 25 per cent; (d) blood pressure 130 to 180 systolic, 80 to 110 diastolic, moderate nitrogen retention (45 to 75 mg. nonprotein nitrogen), albuminuria heavy trace to 10 per cent.

The moderate nephritic group numbered 130 (12.5 per cent). The fetal deaths numbered 44 (33.8 per cent). Excluding three deaths, possibly due to syphilis, 41 cases (31.5 per cent) remain in which the cause of death was the toxemia.

*Severe Nephritis.*—The severe nephritic toxemia generally occurs in multiparas who have had preceding pregnancies with moderate toxemia or a history of a previous nephritis. Occasionally, it arises insidiously in a primipara in whom no predisposing cause can be obtained. It occurs most frequently in the early part of the second trimester and pregnancy frequently terminates about the eighth month. Postpartum the hypertension, if present, persists, and, occasionally, becomes slightly lower. The albuminuria persists for months and sometimes years; a nitrogen retention can almost always be demonstrated soon after delivery. It is generally moderate, although infrequently it precedes a terminal uremia. This is the type of case that has recurrent stillbirths about the sixth or seventh month of pregnancy. The following are the criteria: (a) blood pressure 180 plus systolic, 120 plus diastolic, and albuminuria grading from a heavy trace to a definite percentage; (b) normal blood pressure or any elevation together with an albuminuria exceeding 25 per cent; (c) normal blood pressure or any elevation, albuminuria in amounts from a heavy trace to a percentage with nitrogen retention exceeding 75 mg. per cent nonprotein nitrogen.

The severe nephritic group numbered only 71 (6.8 per cent). The number of dead babies occurring among the 71 patients was 50 (70.4 per cent); excluding one case in which syphilis was present, 49 deaths (69 per cent) resulted from the toxemia.

*Preeclampsia and Eclampsia.*—The third large group comprises the acute toxemias, preeclampsia and eclampsia. These cases start acutely in the last trimester with any of the following: visual disturbances, marked epigastric pain, nausea and vomiting, and generalized edema. The blood pressure may show a gradual rise over a two- to three-week period. Another type, coincidentally with the abruptness of the symptoms, shows a rise of pressure to 170 plus systolic and 110 plus diastolic. The urine contains albumin ranging from a "heavy trace" to a percentage. The eyegrounds are characteristic (spastic vessels, patchy edema of retina and discs, and, not too rarely, detachments of the retina). Postpartum, hypertension and albuminuria disappear very rapidly in a two-week period. The blood chemistry may show an elevation of the uric acid above 4 mg. In the next pregnancy no toxemia may be evident but, in the third and fourth, hypertension or nephritic toxemia in varying degrees of severity are apt to appear.

There were 29 cases of preeclampsia (2.8 per cent) and 63 cases of eclampsia (6 per cent), total cases 92 (8.8 per cent). Among the 29 cases of preeclampsia there were seven dead babies (24.1 per cent) whose death could be attributed only to toxemia. The relatively small number of cases in this series is due to the fact that many cases which might be classified as preeclampsia and which do not strictly follow the above description were included in the nephritic group.

Cases of eclampsia number 63 (6 per cent). The total dead babies in this series was 28 (44.4 per cent); excluding two cases (one birth injury, one congenital abnormality), the corrected number of baby deaths due to toxemia is 26 (41.2 per cent).

There is a remaining group of 10 (0.9 per cent) which cannot be definitely put in either the nephritic or preeclamptic class. The dead babies totalled 4 (40 per cent).

#### INCIDENCE OF PREMATURE BIRTHS

The occurrence of prematurity in the 1,036 cases and in respect to the various types of toxemia is interesting. There were 135 cases (13 per cent) of premature birth (standard was five pounds or less birth weight, or obvious signs of prematurity). Among these, forty died before leaving the hospital. Six babies were born of syphilitic mothers of which 4 lived, and two were born of mothers having uterine fibroids. One baby died whose birth was complicated by a placenta previa. The total corrected number of premature babies, then, is due, apparently, entirely to toxemia.

Prematurity varies markedly with the individual toxemias. This point, because of the small number of cases, is brought out more clearly by percentages as in Table II.

TABLE II. INFLUENCE OF TOXEMIA ON PREMATURE BIRTH

TYPE OF TOXEMIA	NUMBER OF CASES	CASES PRE-MATURITY (CORRECTED)	PREMATURITY PERCENTAGE
Hypertension			
Mild	338	5	1.5
Moderate	197	9	4.5
Severe	50	5	10.0
With late albuminuria	27	12	44.4
Nephritis			
Mild	121	17	14.0
Moderate	130	33	25.4
Severe	71	26	36.6
Preeclampsia	29	7	24.1
Eclampsia	63	9	14.3
Nephritis or preeclampsia	10	3	30.0
Total	1,036	126	

Hypertension with late albuminuria leads all with 44.4 per cent prematurity. Although this group is the second lowest among the entire series in number, the figure must be significant especially when it is compared with the nephritic and the preeclamptic group. The negligible part played by pure hypertension, except when it reaches its highest proportions, is readily seen. Even the most severe grade of hypertension has a 4 per cent lower rate of prematurity than the mild nephritic type. The latter rises rapidly as the severity of the toxemia increases. The severe type almost triples the percentage of the mild type. A comparison of the severe hypertensive and the hypertensive patients showing albuminuria in the seventh and eighth months reveals an astounding difference of prematurity rate. The latter surpasses the former four and one-half times. The presence of albuminuria as an index of serious omen is brought out once again. These two types up until the appearance of albuminuria are extremely alike. So far it has been impossible to judge in the early months which will show albumin in the urine later. It may be that these hypertensive cases with albuminuria had better be classified in the severe nephritic group



but the hypertension is outstanding and persistent. Also the albuminuria in comparison is only temporary. These patients rarely show nitrogen retention and renal function tests at no time give evidence of failure.

The average rate of prematurity for all grades of nephritic toxemia is 25 per cent. Lowest in the mild type with 14 per cent, it climbs rapidly to 36.6 per cent in the severe. Severe nephritic toxemia and hypertensive toxemia with late albuminuria (possibly the same) have an average prematurity rate of 40.5 per cent and are the most potent in causing prematurity.

Preeclampsia leads eclampsia by 10 per cent. Several explanations might be forthcoming for this discrepancy but they would all be valueless in view of the few cases of preeclampsia presented.

The above discussion has dealt with premature babies living and dead. Further facts can be brought out by enumerating the number and percentage of premature live births only.

TABLE III

TYPE OF TOXEMIA	NUMBER OF LIVE BIRTHS	PREMATURE LIVE BIRTHS	PERCENTAGE PREMATURE LIVE BIRTHS
Hypertension			
Mild	319	4	1.2
Moderate	183	9	4.9
Severe	34	5	14.7
With late albuminuria	18	10	55.6
Nephritis			
Mild	101	11	10.9
Moderate	86	25	29.0
Severe	21	14	66.7
Preeclampsia	22	4	18.0
Eclampsia	35	4	11.0
Nephritis or preeclampsia	6	3	50.0
Total	825	89	

Among the 825 babies which lived, 89 (10.7 per cent) were premature. The hypertensive division again was the lowest if we exclude the group showing late albuminuria, demonstrating once more the relative innocuousness to the baby of hypertension as compared with albuminuria. If the nephritic group, 79 (corrected 76), more than doubled the hypertensive group (37, corrected 31) in total prematurity cases, and if the premature babies that died are also compared in groups, then the marked difference is sustained. The nephritic death total (27, corrected 26) was five and one-half to eight times the total of the hypertensive group (5, corrected 3); showing that nephritic toxemia has a more lethal influence on the child than hypertensive.

When the subgroups of the toxemia are compared, it is noted that the mild, moderate, and severe grades of hypertension do not show a proportionately increasing number of prematures as the grade of severity increases. In the nephritic division, a more step-like increase is seen. The preeclampsia and eclampsia groups show, too, an increased premature rate although there is apparently little difference between the two. The number of cases is very small and conclusions would only be presumptive.

If it is considered that nearly all the stillbirths and macerated fetuses credited to the entire series were also premature, then one realizes even

more strongly the etiologic factor of toxemia in the termination of gestation at the seventh and eighth month.

The occurrence of accidental hemorrhage was noted in the study. There were twenty-four cases or 2.3 per cent of the entire series. As has been described previously, no particular toxemia could be selected as a cause. The cases were distributed almost, but not quite, equally between the hypertensive and nephritic group: moderate hypertension 6, severe hypertension 2, severe hypertension with late albuminuria 2, mild nephritis 1, moderate nephritis 9, severe nephritis 4.

The development of psychoses has always been considered pertinent in a study of toxemia. There were twelve cases (1.2 per cent). Five cases occurred in the hypertensive group and seven occurred in the nephritic group.

Twins occurred in thirty-one cases. The cases were scattered but eleven occurred in the mild hypertensive group.

#### DISCUSSION

DR. HENRICUS J. STANDER.—I cannot agree with the classification. It is most essential that we use a uniform classification of the toxemias. Personally, I do not like the term hypertension or essential hypertension, benign or malignant, in connection with the toxemias of pregnancy. I noticed that a large number of these cases reported tonight were grouped as hypertension, mild, moderate, and severe. I feel that some of these patients, if we study them further, may be classified as nephritic, certainly most in the group that the author calls severe hypertension with albuminuria. I believe that patients with toxemia, studied five or ten years later, or over a period of five or more pregnancies, fall into three very simple groups: first, a group which Kellogg calls recurrent toxemia, and which I have called "low reserve kidney." This is a mild type, the patients respond to treatment. In subsequent pregnancies they show no toxemia whatsoever, or they may show the same type of toxemia, and five, six, or seven pregnancies following the first, they show the same type of toxemia or none at all. The second type I feel very definitely is based on kidney damage, nephritis, and the third type is simply the so-called eclamptic group, by which I mean eclampsia and preeclampsia. I regard preeclampsia the same as eclampsia.

I feel that a great deal of confusion has been brought about by the term hypertension, and I would suggest that a national committee be appointed to make a study of the various and different classifications of toxemia to ensure one method of classification.

DR. W. W. HERRICK.—Recently with Dr. Tillman I reported results of a study in which we followed 594 cases of toxemia of pregnancy for from one to fifteen years; the average length of our follow-up being 5.6 years. Certain statistics in this group are startling. The death rate among these 594 cases is four times that expected in women of like age in this community. Eighty per cent of deaths were from causes in the cardiovascular renal field; that is, apoplexy, myocardial failure, or renal failure.

The medical man may properly say a word about the classification of toxemias of pregnancy because of their relation to certain well-known medical disorders. I agree with Dr. Stander that the nephritic group of the toxemias can be set aside as a very definite one. These are merely examples of glomerulonephritis activated or aggravated by pregnancy. They are marked by pronounced and persistent

albuminuria with or without hypertension, a tendency to nitrogen retention, to anemia, and a high fetal mortality, with a surety of recurrence in subsequent pregnancies and a comparatively short life expectancy, with death from uremia or secondary infection.

Another group of toxemias is, in our opinion, allied to hypertensive cardiovascular disease, distinct from nephritis. In this group hypertension is constant but variable. Albuminuria may be absent but when present is abrupt and late in onset and may be slight or large in amount. Nitrogen retention and anemia are absent. There is a vascular rather than an albuminuric type of retinitis. Excepting in the eclampsias there is a lesser tendency to destruction of the fetus. In the follow-up period, the clinical picture is associated with hypertensive cardiovascular disease rather than with nephritis. Death occurs from apoplexy or myocardial failure. In about 10 per cent death occurs as the result of renal arteriosclerosis rather than from primary renal inflammation as in the nephritic group. In this group we find about 80 per cent of all toxemias, including the eclampsias, preeclampsias, and the great group of milder toxemias which are nonnephritic. I believe a good inclusive term for this type is "vascular toxemia." The group of milder nonrecurring toxemias which Dr. Stander calls low reserve kidney, falls into this general vascular group and does not merit a separate classification.

The pathologist is the court of last resort. We are attempting to follow our cases to necropsy. This has been accomplished in 11 instances. In 4, a typical glomerulonephritis was found; in 7 the anatomic evidences of hypertensive cardiovascular disease, among them 3 examples of eclampsia. The remaining 4 were of the milder type often designated preeclamptic or recurring toxemia.

From our follow-up studies in 594 cases and from the limited number of necropsy findings, it seems clear to us that the vascular changes which are characteristic of eclampsia and preeclampsia may not resolve, but in about one-half of the cases continue to develop and in the course of years merge with those characteristic of hypertensive cardiovascular disease.

I agree that a reclassification of the toxemias of pregnancy is desirable. I believe it should be the joint task of the obstetrician, the internist, and the pathologist. Only on the basis of extensive clinical observation, prolonged follow-up and necropsy studies, can a logical classification be worked out. When this is done, I believe it will be found that we have two leading types of toxemia; the first, a smaller group characterized by glomerulonephritis; the second, related in etiology and course to primary cardiovascular disease with hypertension.

DR. HARRY ARANOW.—Without going into the merits of the different classifications of toxemia, one point that seems to me worth while is that it is not worth while risking the life of the mother to try to save that of the baby, because the baby so often is lost. I think when the case is serious, it is better to terminate labor without waiting too long.

DR. BENJAMIN P. WATSON.—I think the other point that arises, along the same line that Dr. Aranow referred to, is the question of terminating pregnancy early in these cases. I think we are very often hesitant in terminating pregnancy early, and in view of the figures we have had in regard to the poor chance of the child, I think those figures should help us in many cases to determine the early termination of perhaps more pregnancies than we do at present.

# AN ANALYSIS OF 127 CASES OF ECLAMPSIA TREATED BY THE MODIFIED STROGANOFF METHOD

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FROM the date of its inception in 1896 to Feb. 15, 1933, 384 cases of typical eclampsia have been observed and treated on the Obstetrical Service of the Johns Hopkins Hospital. During these thirty-six years, marked changes have occurred in the policy of the clinic in regard to the routine therapy for such patients. In the early years extremely radical procedures were employed when the convulsive attack occurred prior to delivery, accouchement forcé and vaginal hysterotomy, in later years supplemented by abdominal section. However, beginning in 1912, radical procedures were gradually given up and were supplanted by more conservative measures which did not aim at the immediate delivery of the patient. The experience of the clinic during these years and the results obtained have been well summarized in the contributions of Wilson in 1925, and Williams in 1927. On Oct. 15, 1924, a routine treatment for cases of eclampsia, new to the clinic, was instituted, the modified Stroganoff method, and this program of therapy has been consistently followed from that time to the present. The details of this treatment as employed at the Johns Hopkins Hospital were set forth in an article by Stander in 1925 and comprise essentially the conservative procedures of Stroganoff, although amended by Stander to exclude the use of chloroform and venesection.

During the eight and a third years elapsing since the institution of the above policy, 127 cases of typical eclampsia have been observed on the hospital service and uniformly treated by this method. It is believed that these cases comprise a large enough series so that the results may be analyzed and compared with those obtained with previous forms of therapy. It is also our purpose to discuss the mortality rates obtained in their relation to certain clinical phenomena occurring in the disease.

An examination of the case records of the entire series of eclamptic patients indicates that a division into four time periods so far as therapy is concerned may well be made. From 1896 to the end of 1911 the treatment was extremely "radical," as only two out of 85 patients with ante or intrapartum eclampsia were allowed to deliver spontaneously. During the next seven years a period of "transition" occurred with an ever increasing tendency toward conservative meas-

ures. From 1919 to Oct. 15, 1924, various conservative therapeutic measures were employed, but in no instance was forceful delivery of the patient carried out. This period may be termed "conservative," and it is noteworthy that liberal use of venesection was made during this time. The last period, from Oct. 15, 1924, to the present, comprises the "modified Stroganoff" era.

TABLE I. ECLAMPSIA TREATED BY MODIFIED STROGANOFF THERAPY OCT. 15, 1924, TO FEB. 15, 1933 (EIGHT YEARS, FOUR MONTHS)  
CASES OF TYPICAL ECLAMPSIA, 127

	NO. CASES	MA- TERNAL DEATHS	FETAL DEATHS	MA- TERNAL MORTAL- ITY PER CENT	TOTAL FETAL MORTAL- ITY PER CENT	FETAL MORTALITY EXCLUDING P. P. ECLAMPSIA
Total eclampsia	127	14	50	11.02	39.37	51.09
Mild eclampsia	70	2	22	2.86	31.43	41.67
Severe eclampsia	57	12	28	21.05	49.12	61.36
Antepartum eclampsia	56	7	39	12.50	69.64	
Intrapartum eclampsia	36	2	8	5.56	22.22	
Postpartum eclampsia	35	5	3	14.29	8.57	
Antepartum, mild	26	2	15	7.69	57.67	
Intrapartum, mild	22	0	5	0.00	22.73	
Postpartum, mild	22	0	2	0.00	9.09	
Antepartum, severe	30	5	24	16.67	83.33	
Intrapartum, severe	14	2	3	14.29	21.43	
Postpartum, severe	13	5	1	38.46	7.69	

The results obtained in the treatment of eclampsia by the modified Stroganoff method are portrayed in Table I. The gross maternal mortality for the entire series was 11.02 per cent, a figure which, as will be shown subsequently, is significantly lower than that obtained under other forms of therapy.

In 1922, Thomas Watts Eden suggested that the results of treatment varied greatly with the severity of the disease and laid down the following criteria for differentiating between the mild and severe cases: (a) a temperature above 103° F., (b) a pulse rate over 120, (c) a blood pressure of 200 mm. or over, (d) an urine which solidifies on boiling, (e) absence of edema, (f) persistent coma, (g) more than ten convulsions. If two or more of the above symptoms or signs are present, the case is to be classified as severe; and as mild when none or only one of them is present. When the above cases were divided into "mild" and "severe" according to the criteria suggested by Eden, it was found that the mortality rates were 2.86 and 21.05 per cent, respectively. Only two deaths occurred among 70 cases of mild eclampsia, both of them in the antepartum variety. However, a fatal outcome ensued in more than a fifth of those cases classified as severe, and although this is an improvement as contrasted with results attained previously, yet such a mortality remains an appalling one. It is interesting to note that in contrast with an apparently widespread

belief to the contrary, postpartum eclampsia in our series resulted in a higher mortality (14.29 per cent) than either the antepartum or intrapartum types (12.50 and 5.56 per cent, respectively). As was to be expected the fetal mortality, excepting postpartum cases, was high throughout. However, it was somewhat lower than that attained previously, even under radical therapy with immediate delivery of the child.

TABLE II. RESULTS IN 384 CASES OF ECLAMPSIA

THERAPY		TOTAL CASES	GROSS MATERNAL MORTALITY PER CENT	GROSS FETAL MORTALITY PER CENT*
Period 1	Radical 1896-1911	110	22.8	57.6
Period 2	Transition 1912-1916	71	16.9	59.6
Period 3	Conservative 1919-Oct. 14, 1924	76	14.6	63.9
Period 4	Stroganoff Oct. 15, 1924-Feb. 15, 1933	127	11.0	51.1

\*Excluding postpartum eclampsia.

TABLE III. MORTALITY PERCENTAGE, FOUR TIME PERIODS

	PERIOD 1	PERIOD 2	PERIOD 3	PERIOD 4
Total Cases				
Mild	10.9	3.4	0.0	2.9
Severe	39.1	26.2	27.5	21.1
Total	22.8	16.9	14.6	11.0
Antepartum				
Mild	15.2	0.0	0.0	7.7
Severe	35.7	24.1	22.7	16.7
Total	24.6	18.9	11.4	12.5
Intrapartum				
Mild	12.5	9.1	0.0	0.0
Severe	50.0	22.2	25.0	14.3
Total	25.0	15.0	13.3	5.6
Postpartum				
Mild	0.0	0.0	0.0	0.0
Severe	40.0	50.0	40.0	38.5
Total	16.0	14.3	23.5	14.3

Tables II and III afford a comparison of the results to mother and child during the four periods of therapy as previously outlined. It will be noted that the maternal mortality rate under Stroganoff is approximately half that resulting from the old radical treatment. It is even somewhat lower than when the conservative methods in use previously were employed. A careful analysis of the case records would seem to indicate that there are only two main differences in therapy during these past two periods, namely that the use of venesection has been entirely discarded and that intravenous glucose is now rather liberally used.

Tables II and III would seem to indicate definitely the advantages of conservative over radical procedure in the treatment of eclampsia, and most particularly so far as the mild type of case is concerned.

The results in the severer cases are far from satisfactory but still represent an improvement over any line of treatment hitherto employed by us. Finally we wish to emphasize that the only type of eclampsia whose death rate remained unchanged throughout the entire period of time is the severe postpartum variety, and it is this type of case which would be least influenced by the changing methods of treatment.

The case records of those 127 eclamptic women treated by the Stroganoff method were carefully analyzed in order that the maternal mortality might be correlated with various clinical factors coincident to the condition. The results of this analysis are shown in Table IV. IV.

TABLE IV. MATERNAL MORTALITY IN TERMS OF RACE, AGE, AND PARITY OF PATIENT

RACE			AGE		
	CASES	MORTALITY PER CENT		CASES	MORTALITY PER CENT
White	61	13.11	-16 yr.	15	6.67
Colored	66	9.09	17-19 yr.	40	5.00
			20-34 yr.	54	20.37
			35 yr. and over	18	0.00

PARITY		
	CASES	MORTALITY PER CENT
Para 0	84	8.33
Para i and ii	17	17.65
Para iii, iv, and v	18	22.22
Para vi and over	8	0.00

Table IV indicates the maternal mortality in terms of the race, age, and parity of the patient. It will be noted that the cases are about equally divided between the black and white races, with the maternal mortality somewhat higher in the latter group. In our experience the prognosis in eclampsia was best in the young woman under twenty years of age and pregnant for the first time. Conversely a high death rate prevailed in those patients aged twenty to thirty-four years and among multiparas of less than 6 pregnancies. It is interesting that there were eighteen cases of eclampsia without a single death in women of thirty-five years and over, eight of whom had had 6 or more previous pregnancies. Fourteen of these women returned a year or more after delivery for reexamination and all but one were found to have definite signs of chronic nephritis. It seems probable that most of the cases in this group were instances of "eclampsia superimposed on chronic nephritis," and it is our experience that the immediate prognosis in this type of case is favorable, although the remote one very gloomy.

## PROGNOSIS IN ECLAMPSIA ACCORDING TO EDEN'S CLASSIFICATION

*A. Temperature and Pulse.*—That there is a direct correlation between the maternal mortality and rising temperature and pulse rate is indicated by Table V. Our experience confirms closely Eden's finding that a temperature of 103° F. and above and a pulse rate over 120 are associated with a grave prognosis to the patient.

TABLE V. MATERNAL MORTALITY IN TERMS OF TEMPERATURE AND PULSE OF PATIENT (MAXIMUM)

TEMPERATURE	CASES	MORTALITY PER CENT	PULSE	CASES	MORTALITY PER CENT
- 99.9	57	7.02	- 89	14	0.00
100-102.9	46	4.35	90-119	63	6.35
103-104.9	19	21.05	120-149	38	10.53
105 and over	5	80.00	150 and over	12	50.00

TABLE VI. MATERNAL MORTALITY IN TERMS OF BLOOD PRESSURE AND ALBUMINURIA (MAXIMUM)

SYSTOLIC PRESSURE	CASES	MORTALITY PER CENT	DIASTOLIC PRESSURE	CASES	MORTALITY PER CENT
-159	11	0.00	-119	50	12.00
160-179	35	5.71	120-139	53	15.10
180-199	32	15.63	140 and over	24	0.00
200-219	28	21.43			
220 and over	21	4.76			

## ALBUMINURIA

	CASES	MORTALITY PER CENT
Less than 1 gram	21	14.29
1-9.9 grams	72	5.55
10 grams and over	30	10.00
Unknown	4	----

*B. Blood Pressure and Albuminuria.*—Eden stated in his classification of eclampsia that when the systolic blood pressure was over 200 mm., or the urine contained sufficient albumin to render it solid on boiling, it indicated a more serious prognosis for the given case. In this clinic it has long been the custom to estimate the amount of albumin quantitatively by the Esbach method in terms of grams per liter and also to assume that 10 grams would be the approximate equivalent of an amount necessary to render urine "solid on boiling."

Table VI shows that in our experience 180 mm. systolic pressure would afford a better dividing line between a mild or severe type of case than 200 mm. On the other hand the degree of elevation of the diastolic pressure seemed to afford no criterion as to the severity of the case. It is interesting to note that only one death occurred in 21 women whose systolic pressure was 220 or over and not a single fatal-



ity was experienced in 24 whose diastolic pressure was 140 or above. It seems probable that many of these cases were instances of the previously mentioned "eclampsia superimposed on chronic nephritis." Finally, it will be noted from Table VI that the amount of albuminuria present gave no indication of the ultimate outcome of the disease.

*C. Convulsions, Coma, and Edema.*—Table VII indicates that the prognosis of a case of eclampsia becomes grave whenever the coma is deep and prolonged or edema lacking or very slight. Furthermore it will be noted that among those 18 patients whose eclampsia was characterized by only one convulsion not a single fatality ensued. Also

TABLE VII. MATERNAL MORTALITY IN TERMS OF CONVULSIONS, COMA, AND EDEMA OF PATIENT

COMA			EDEMA		
	CASES	MORTALITY PER CENT		CASES	MORTALITY PER CENT
Slight	65	1.54	None or Slight	46	21.74
Moderate	30	3.33	Moderate or Marked	77	5.19
Prolonged	32	37.50	Unknown	4	----

CONVULSIONS		
	CASES	MORTALITY PER CENT
1	18	0.00
2- 4	40	10.00
5- 9	31	9.68
10-19	21	9.52
20 and over	17	29.41

the mortality remained unchanged and was approximately 10 per cent when from two to twenty convulsions occurred but was three times as high when the number of fits was above the latter figure.

Careful analysis of the 127 cases of eclampsia comprising this series indicates that from our experience certain modifications might be made in Eden's classification which would give a more accurate conception of the mildness or severity of a given case. Four of his criteria of severity we leave essentially unaltered; namely, prolonged coma, a pulse rate of 120 or over, temperature of 103° F. or above, and edema either absent or very slight. In our experience there was no correlation between mortality and the amount of albuminuria, and this item is omitted entirely. Furthermore we would amend the last two items so that a blood pressure of 180 and above instead of 200 be considered an indication of severity and also stipulate that 20 fits instead of 10 be made the dividing line for this item.

In order to test the validity of our proposed modification we have reexamined the case records of the last 205 eclamptic women observed in the clinic and have classified them as mild or severe according to the above schedule (Table VIII).

From Table VIII it would seem evident that the suggested modified classification affords a relatively exact fit with our experience with eclampsia treated by conservative methods.

Furthermore we have analyzed these 205 cases and related the maternal mortality to the total number of positive criteria of severity found in each instance. Those cases with none or one positive item are of course classified as mild, and in them (102) not a single maternal death occurred. However, as the number of positive criteria

TABLE VIII. RESULTS IN 205 CASES OF ECLAMPSIA ACCORDING TO PROPOSED MODIFIED CLASSIFICATION

	CASES	MATERNAL DEATHS	MORTALITY PER CENT
Antepartum, mild	45	0	0.00
Intrapartum, mild	29	0	0.00
Postpartum, mild	28	0	0.00
Antepartum, severe	55	12	21.82
Intrapartum, severe	24	4	16.67
Postpartum, severe	24	9	37.50
Total mild eclampsia	102	0	0.00
Total severe eclampsia	103	25	24.27

TABLE IX. RELATION OF RESULTS IN ECLAMPSIA TO NUMBER OF POSITIVE CRITERIA FOUND ACCORDING TO PROPOSED MODIFIED CLASSIFICATION

POSITIVE CRITERIA	CASES	MATERNAL DEATHS	MORTALITY PER CENT
0	29	0	0.00
1	73	0	0.00
2	34	3	8.82
3	29	4	13.79
4	25	9	36.00
5	10	5	50.00
6	5	4	80.00

TABLE X. LABOR IN ANTEPARTUM AND INTRAPARTUM CASES

	CASES	
Labor spontaneous	38	
Labor operative	48	
Forceps		39
Breech extraction		2
Version		1
Craniotomy		3
Cesarean section		3
Died undelivered	5	
Unknown	1	

increase we find a rapidly rising maternal mortality rate, and it will be noted that when 4 or more factors of severity are present the mortality risk becomes 45 per cent.

Table X is included to illustrate the uniformly conservative therapy employed in the cases of the series so far as efforts at termination of the pregnancy were concerned. It should be stated that out of 56 cases of antepartum eclampsia encountered, labor was induced forty-

eight hours or more after the subsidence of the convulsive attack in 26 instances, the remaining falling into labor spontaneously. The various operative procedures detailed were of course done only after complete and spontaneous cervical dilatation had been reached. Craniotomy was employed in three instances where it seemed reasonably certain that fetal death in utero had occurred some time before. It will be noted that cesarean section was practiced on three patients, and in each case the indication for the operation was pelvic dystocia.

#### SUMMARY

From Oct. 15, 1924, to Feb. 15, 1933, a total of 127 cases of typical eclampsia have been observed on the Obstetrical Service of the Johns Hopkins Hospital and routinely treated by the "modified Stroganoff" method. In this series there were fourteen maternal deaths, a mortality of 11.02 per cent. The highest death rate prevailed in the post-partum variety of the disease, and the lowest in the intrapartum. The mortality rates during the Stroganoff regime were lower than at any other period of the thirty-seven years of the clinic's existence, during which time the therapeutic policy has gradually swung from extremely radical to equally conservative methods. Indeed the death rate here given is less than half that obtained under the old radical forms of treatment. Dividing the cases into "mild" and "severe" types according to the classification of Eden, the maternal mortality was 2.86 and 21.05 per cent, respectively.

As a result of careful analysis of the above 127 cases of eclampsia, it was found that the following "modified classification" of mildness or severity in our experience gave a more exact criterion as to prognosis than Eden's original one. (1) Temperature of 103° F. or above, (2) pulse rate of 120 or over, (3) blood pressure (systolic) of 180 or over, (4) no or very slight edema, (5) deep and persistent coma, and (6) 20 or more convulsions. If two or more of these criteria occur the case is to be classified as severe.

A test of this proposed schedule in 205 consecutive cases of eclampsia resulted in 102 being classified as mild with no deaths and 103 severe with 25 deaths, or 24.27 mortality per cent. Moreover, our findings indicate a very direct correlation between the number of positive criteria of severity and the mortality risk rate.

A somewhat higher death rate was noted among the blacks than the whites in the series. Also the young woman below the age of twenty and the primipara seemed to have a more favorable prognosis than the woman in the older stages of her child-bearing career or one who had had previous pregnancies.

From the foregoing discussion it seems evident that the modified Stroganoff method offers better results in the treatment of eclampsia than any hitherto tested by us. Indeed one can safely say that in the

milder cases the results are quite satisfactory. However, in the severe type of case the mortality under this regime is still extremely high, although more favorable than under any form of treatment previously used. Obviously, as Williams has stated, "the treatment of eclampsia must remain empiric and relatively unsatisfactory until the actual cause of the disease is discovered." We believe, however, that at the present time the modified Stroganoff treatment offers as good results as any variety in vogue. Quite possibly it is little if any better than certain other essentially conservative procedures that have been suggested, such as that with magnesium sulphate. However, it seems evident that the average patient is much better off the more she is left alone. It is possible, however, that in certain of the more severe cases in which the patients seem to be becoming worse under conservative procedures, and in whom spontaneous delivery will not shortly occur, cesarean section under local or spinal anesthesia might offer more favorable results. If acidosis develops the liberal use of intravenous glucose, with or without insulin, seems definitely beneficial. In our experience, venesection is of no definite value. Finally, it seems important to avoid, so far as is possible, the use of inhalation anesthetics for any type of operative procedure which may become necessary.

#### CONCLUSIONS

1. The maternal mortality in 127 cases of typical eclampsia treated by the modified Stroganoff method was 11.02 per cent. This was a lower figure than previously attained at the Johns Hopkins Hospital by other forms of therapy.

2. The maternal mortality was somewhat higher in the white than the black race. Also it was increased in the multiparous woman and in one in the older stages of the child-bearing career.

3. A modification of Eden's classification for determining the severity of a given case is suggested. This, in our experience, gave a more accurate prognosis than did the original.

4. The modified Stroganoff treatment gives quite satisfactory results in the mild form of case. In severe cases it is preferable to the old forms of radical treatment but is still followed by a high mortality, 24.27 per cent. In the latter type of case, becoming worse under conservative therapy, cesarean section under local or spinal anesthesia seems permissible.

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# STUDIES OF HEPATIC FUNCTION

## IV. HEPATIC FUNCTION DURING PREGNANCY

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**S**TUDIES of hepatic function during normal pregnancy have yielded conflicting results. This has been particularly true of data based upon studies of the glycogenic function of the liver, the urinary nitrogen partition, and the Widal hemoclastic crisis. Many such studies have apparently indicated some degree of hepatic functional impairment in many cases but, in the light of present-day views regarding the lack of specificity of these methods, the significance of these findings is questionable. The general opinion at the present time is that the most reliable available tests of the functional capacity of the liver are those which deal with its excretory function, particularly with regard to the elimination of bilirubin and certain dyes, the one most commonly employed being bromsulphalein.

The present study consists of the determination of the serum bilirubin concentration and of the degree of bromsulphalein retention in a series of 34 normal pregnant women, 26 women with varying grades of toxemia of pregnancy and 8 presenting some other complication during pregnancy; similar studies were made in 15 of these cases twenty-four hours after delivery, in 12 instances with, and in 3 without anesthesia. The serum bilirubin determinations were made by the Thannhauser-Andersen modification of the van den Bergh procedure; as stated in a previous report,<sup>1</sup> in our experience the normal range of serum bilirubin is from 0.1 to 1.0 mg. per 100 c.c. by this method. The 2 mg. per kilogram dosage of bromsulphalein was employed, determinations being made thirty minutes following injection of the dye; in the absence of hepatic functional impairment, no dye should remain in the blood stream at the end of thirty minutes.

### RESULTS OF PRESENT STUDY

*Normal Pregnancy (Table I).*—In this group of 34 cases, the serum bilirubin concentration varied from 0.2 to 1.0 mg. per 100 c.c. Studies were made at term in 29 cases, during the seventh month in 2, the fifth in 1, and the third in 2 cases. Normal results were obtained with the bromsulphalein test in 26 cases, 8 showing dye retention of from 5 to 20 per cent at the end of thirty minutes. The case with

20 per cent retention was a multigravida (8) in the seventh month of gestation; the others (5 to 10 per cent retention) were studied at term, 3 being primigravidas and 4 multigravidas (2-13).

TABLE I. NORMAL PREGNANCY

PATIENT	MONTH	GRAVIDA	SERUM BILIRUBIN (MG. PER 100 C.C.)	BROMSULPHALEIN RETENTION PERCENTAGE
F. S.	3	2	0.64	0
P. K.	3	4	1.0	0
H. W.	5	1	0.4	0
E. J.	7	1	0.28	0
J. J.	7	8	0.88	20
M. G.	9	1	0.48	0
H. K.	9	4	0.56	0
N. W.	9	6	1.0	0
A. P.	9	2	0.44	0
V. K.	9	3	0.37	0
B. W.	9	1	0.37	0
M. D.	9	1	0.6	0
W. Y.	9	1	0.2	0
V. McC.	9	1	0.4	0
M. G.	9	12	0.52	0
F. V.	9	1	0.35	0
E. R.	9	1	0.36	0
L. R.	9	1	0.3	0
R. V.	9	4	0.28	0
A. G.	9	4	1.0	0
E. M.	9	1	0.72	0
E. W.	9	1	0.52	0
L. B.	9	2	0.52	0
A. G.	9	1	0.56	0
L. R.	9	1	0.4	0
I. K.	9	9	0.57	0
M. M.	9	9	0.29	0
C. J.	9	2	1.0	5
L. G.	9	2	1.0	5
C. Z.	9	1	0.3	10
B. T.	9	3	0.24	10
J. B.	9	13	0.88	10
D. D.	9	1	0.8	10
R. DeM.	9	1	0.56	5

*Toxemia of Pregnancy (Table II).*—This group consisted of 2 patients with eclampsia (classified as severe toxemia), 4 with preeclamptic toxemia (classified as moderate toxemia), and 20 with mild toxemia, characterized by moderate grades of hypertension, nausea, and vomiting. In the two patients with eclampsia the serum bilirubin concentration was 1.08 and 0.8 mg., respectively, with bromsulphalein retention of 60 and 20 per cent, respectively. The four women with preeclamptic toxemia showed serum bilirubin values of 0.85, 1.2, 2.2, and 2.8 mg. and dye retention of 0, 0, 30, and 30 per cent, respectively. In the group of 20 patients with mild toxemia the serum bilirubin concentration ranged from 0.24 to 0.8 mg. per 100 c.c.; dye retention (10, 15, and 30 per cent) was present in three instances. The blood nonprotein nitrogen and blood sugar were within normal limits in every case.

*Other Complications (Table III).*—In 4 patients with chronic nephritis complicating pregnancy (NPN 49.2 to 76.4 mg. per 100 c.c.) the serum bilirubin concentration ranged from 0.54 to 1.2 mg. per 100 c.c.; dye retention (5 per cent)

TABLE II. TOXEMIA OF PREGNANCY

PATIENT	MONTH	GRAVIDA	SERUM BILIRUBIN (MG. PER 100 C.C.)	BROMSULPHALEIN RETENTION PERCENTAGE	CONDITION
C. H.	9	1	1.08	60-	Severe
E. K.	9	1	0.8	20	Severe
E. C.	3	7	0.85	0	Moderate
M. M.	5	9	1.2	0	Moderate
M. R.	7	1	2.8	30	Moderate
K. M.	3	2	2.2	30	Moderate
G. P.	6	1	1.00	0	Mild
M. B.	7	4	0.4	0	Mild
V. N.	7	2	0.66	0	Mild
E. S.	9	2	0.33	0	Mild
A. G.	9	6	0.36	0	Mild
J. W.	9	2	0.36	0	Mild
R. R.	9	8	0.24	0	Mild
A. Si.	9	1	0.25	0	Mild
A. St.	9	3	0.52	0	Mild
M. S.	9	1	0.76	0	Mild
O. E.	9	2	0.29	0	Mild
C. M.	9	1	0.66	0	Mild
M. J.	9	8	0.52	0	Mild
M. H.	9	4	0.56	0	Mild
R. R.	9	4	0.56	0	Mild
A. M.	9	10	0.25	0	Mild
E. B.	9	6	0.8	0	Mild
C. H.	9	4	0.35	15	Mild
L. P.	9	3	0.52	30	Mild
C. S.	9	1	0.38	10	Mild

TABLE III. COMPLICATED PREGNANCY

PATIENT	MONTH	GRAVIDA	SERUM BILIRUBIN (MG. PER 100 C.C.)	BROMSUL- PHALEIN RETENTION PERCENTAGE	CONDITION
R. O.	9	9	0.88	0	Chronic nephritis
E. K.	7	12	0.6	5	Chronic nephritis
A. C.	9	5	0.54	5	Chronic nephritis
R. M.	9	1	1.2	0	Chronic nephritis
L. P.	9	2	0.35	5	Pyelitis
V. S.	9	8	0.5	15	Pyelitis
M. T.	4	4	0.71	5	Carcinoma of ovary
G. B.	6	2	0.25	0	Syphilis

was present in 2 of these cases. In 2 patients with pyelitis the serum bilirubin was 0.35 and 0.5 mg. per 100 c.c., with dye retention of 5 and 15 per cent, respectively. One patient with carcinoma of the ovary had a serum bilirubin concentration of 0.71 mg. with dye retention of 5 per cent and in one with tertiary syphilis the serum bilirubin concentration was 0.25 mg. per 100 c.c., with no dye retention.

*Effect of Delivery and Anesthesia (Table IV).*—Studies were made in 15 cases before and twenty-four hours after delivery. In 3 instances no anesthetic was employed; the serum bilirubin concentration was unchanged in 1, rose slightly in 1, and fell slightly in the other. In 1 case with 60 per cent retention of bromsulphalein antepartum (eclampsia), there was only 30 per cent retention after delivery. The details regarding the type and quantity of anesthetic administered to the other patients in this group are presented in Table IV. The serum bilirubin concentration

rose appreciably in 5 cases, fell appreciably in 4, and remained essentially unchanged in 3 instances; in no patient receiving an anesthetic, however, was it above the upper limit of normal either before or after delivery. In 1 case (L. R.) with no antepartum retention of bromsulphalein, 60 per cent retention was present postpartum. In 2 others (E. K. and B. T.) with 20 and 10 per cent retention antepartum, respectively, this retention was increased to 80 and 15 per cent after delivery. Two others (J. B. and C. Z.) with 10 per cent retention and the remaining 7 with no retention remained unaltered.

TABLE IV. EFFECT OF DELIVERY AND ANESTHESIA

PATIENT	ANESTHESIA	DELIVERY	SERUM BILIRUBIN (MG. PER 100 C.C.)		BROMSULPHALEIN RETENTION PERCENTAGE	
			BEFORE	AFTER	BEFORE	AFTER
C. H.	None	Spont.	1.08	0.96	60	30
R. R.	None	Spont.	0.24	0.24	0	0
V. McC.	None	Spont.	0.4	0.68	0	0
V. K.	Chlorof. 20 minims	Spont.	0.37	0.82	0	0
A. P.	Chlorof. 20 minims	Spont.	0.44	0.3	0	0
B. W.	Chlorof. 30 minims	Spont.	0.37	0.39	0	0
E. K.	Chlorof. 240 minims	Forceps	0.8	0.68	20	80
J. W.	Chlorof. 30 minims	Spont.	0.36	0.35	0	0
J. B.	Chlorof. 60 minims	Spont.	0.88	0.56	10	10
C. Z.	Chlorof. 240 minims	Forceps	0.3	0.65	10	10
L. R.	Chlorof. 60 minims	Forceps	0.3	0.78	0	60
W. Y.	Chlorof. 60 minims	Forceps	0.2	0.44	0	0
M. G.	Ether $\frac{1}{2}$ oz.	Spont.	0.48	0.35	0	0
B. T.	Ether 8 oz.	Section	0.24	0.44	10	15
G. B.	Ether 10 oz.	Forceps	0.25	0.29	0	0

## DISCUSSION

Several authors, including Schmidt,<sup>2</sup> Mikeldadse,<sup>3</sup> Breda<sup>4</sup> and Eufinger and Bader,<sup>5</sup> believe that normal pregnancy is accompanied by a mild degree of hyperbilirubinemia. However, the values reported by these observers are rarely above 0.7 mg. per 100 c.c. and should, in our experience, be considered to be within normal limits. Murchison<sup>6</sup> believed that pressure of the gravid uterus upon the extrahepatic bile ducts might cause hyperbilirubinemia, but this seems highly improbable. Westphal<sup>7</sup> suggested that a state of physiologic vagotonia may exist during pregnancy and that the heightened excitability of the vagus may produce spasm of the bile ducts, biliary stasis, and hyperbilirubinemia. As stated by Barron,<sup>8</sup> these theoretical concepts have received no experimental or clinical support. The data reported here support the belief that the serum bilirubin concentration remains within normal limits during the course of normal pregnancy.

In spite of this and similar observations, however, there is some rather definite evidence that the capacity of the liver for eliminating bilirubin is somewhat diminished during the period of gestation. Kaufmann<sup>9, 10</sup> found that 8 of 16 women showed an abnormal delay in the excretion of intravenously injected bilirubin. Soffer<sup>11</sup> studied 21 normal pregnant women by the same method, i.e., the bilirubin excretion test. Eleven of these were studied during the first four months of gestation, only 1 of whom showed an abnormal response. On the other hand, abnormal findings were obtained in 9 of 10 women studied during the last five months of pregnancy. Of 10 patients studied during both the first and the second half of pregnancy, 8 showed increased delay in the elimination of bilirubin during the latter period. Hyperbilirubinemia was apparently not present in any case in this series.



As stated previously, other tests of hepatic function have yielded conflicting results. Walthard,<sup>12, 13</sup> investigating the degree of urobilinuria, among other things, concluded that there is some impairment of liver function during labor but not during pregnancy. Rosenfeld and Schneiders<sup>14</sup> obtained normal results with the phenoltetrachlorophthalein test in 6 normal pregnant women, while Smith<sup>15</sup> reported occasional slight dye retention in a group of 20 normal pregnant women. Normal findings were obtained with the bromsulphalein test by Siegel<sup>16</sup> in 62 patients and by Freiheit<sup>17</sup> in 20 cases, the latter being in the last month of pregnancy. In the present series of 34 normal cases, retention of bromsulphalein of from 5 to 20 per cent was observed in 8 instances (23.5 per cent). This comparatively high incidence of hepatic functional impairment is probably due to the relatively small number of cases in this group, but the same may be said of the negative findings reported by other observers. Although of no real statistical value, these observations are, we feel, of definite significance so far as they add material support to the belief in the existence of some disturbance of hepatic function during the latter half, at least, of normal gestation. It may be mentioned that Huwer<sup>18</sup> states that hepatic function tests based on the ability of that organ to eliminate dyes are not applicable during pregnancy because of alterations in the protein content of the blood plasma. In our opinion, however, there is no substantial evidence that the latter factor exerts any significant influence upon the elimination of bromsulphalein.

The majority of investigators of this subject agree that some disturbance of liver function, if not actual liver damage, is a common manifestation of the toxemia of pregnancy. There seems little doubt that the severe forms of this condition, commonly designated eclampsia gravidarum, are associated with, if not dependent upon, varying degrees of acute or subacute hepatic necrosis. According to Hofbauer,<sup>19, 20</sup> as a result of increase in the size of the gravid uterus, there develop (1) stasis in the central veins of the liver lobules, (2) disappearance of glycogen and its replacement by fat droplets, and (3) biliary stasis. He believes that these changes are accompanied by evidence of hepatic functional impairment, as indicated by urobilinuria, alimentary levulosuria, and delayed elimination of intravenously injected bilirubin. These changes, constituting what Hofbauer terms the "liver of pregnancy," represent, according to him, the initial anatomic basis for the development of eclampsia. Similarly, Paramore<sup>21</sup> believes that marked dilatation of the venules of the hepatic lobules, particularly the central veins, constitute the fundamental pathologic lesion of eclampsia. It is doubtful, however, that marked circulatory changes in the liver can result merely from the increased intraabdominal pressure caused by the gravid uterus.

Eufinger and Bader<sup>5</sup> reported a positive direct van den Bergh reaction in 8 of 20 cases of hyperemesis gravidarum and in 8 of 15 cases of eclampsia. Barron<sup>8</sup> states that all authors agree that the estimation of the serum bilirubin concentration in such patients is of great prognostic value since the degree of hyperbilirubinemia parallels the gravity of the symptomatic manifestations. Heynemann<sup>22</sup> advised that all pregnant women with serum bilirubin concentrations above 1 mg. per 100 c.c. should be watched carefully. In the present series there were 20 patients with mild toxic manifestations consisting of slight hypertension, moderate nausea and vomiting, albuminuria and, occasionally, edema. The serum bilirubin concentration was within normal limits in every case. Hyperbilirubinemia was present in 3 of 4 cases regarded as moderately toxic (preeclamptic) and in 1 of 2 cases of eclampsia. Contrary to the statement made by Barron, there was no apparent relationship between the degree of bilirubinemia and the severity of the toxic manifestations. The direct van den Bergh reaction was negative in every instance.

Several authors have emphasized the value of the bromsulphalein and other dye tests in the diagnosis of the toxemias of pregnancy. Smith<sup>15</sup> reported impairment of elimination of phenoltetrachlorophthalein in 20 of 44 toxic patients; he concluded that dye retention indicates severe toxemia but that the degree of retention is not proportional to the extent of liver damage. A similar opinion was expressed by Naujoks.<sup>23</sup> Krebs and Dieckmann<sup>24</sup> obtained variable findings in a group of 37 women with toxemia of pregnancy, none of whom was suffering with eclampsia. The majority showed a moderate degree of dye retention, some showed no retention, and a few were markedly abnormal. Positive findings were usually obtained in two types of patient: (1) those with hypertension but no toxic symptoms and (2) those with toxic symptoms but no hypertension. Rosenfeld and Schneiders<sup>14</sup> reported dye retention in 7 patients with hyperemesis gravidarum and in 9 with hypertension. King<sup>25</sup> made the following observations regarding bromsulphalein retention in the toxemia of pregnancy: (1) no retention in 11 cases without convulsions; (2) from a trace to 25 per cent retention in 7 of 10 cases of eclampsia; (3) from 10 to 25 per cent retention in 3 cases of hyperemesis gravidarum. Trainor<sup>26</sup> noted dye retention in 2 women with postpartum eclampsia. Siegel<sup>16</sup> reported the following findings: from 1 to 3 per cent bromsulphalein retention in 17 toxic patients without hypertension; from 1 to 3 per cent retention in 6 cases of eclampsia; very slight retention (1 per cent) in 2 patients with hyperemesis gravidarum. The following observations were made by Freiheit<sup>17</sup>: of 7 patients with hyperemesis gravidarum, 2 showed dye retention, one with 10 per cent retention dying in four weeks with acute yellow atrophy of the liver, the other, with 20 per cent retention, giving a normal response three days postpartum; of 13 cases with hypertension, albuminuria, and edema (kidney of pregnancy), 4 showed a trace and 2 showed 5 per cent retention; of 11 cases with convulsions, 3 showed 15 per cent and 1 showed 20 per cent retention. Freiheit concluded that whereas this procedure may be of value in determining the degree of toxemia in hyperemesis gravidarum, it is not of value either in predicting the outcome or in differentiating nephritic from eclamptic toxemia. In this latter statement he differs from the majority of authors who believe that dye retention is usually present in eclampsia and is uniformly absent in nephritis.

In the present series, retention of bromsulphalein (20 and 60 per cent) was present in both patients with eclampsia, in 2 of 4 moderately toxic patients (30 per cent), and in 3 of 20 mildly toxic patients (10, 15, and 30 per cent). All patients recovered. Retention of 5 per cent was also noted in 2 of 4 cases of chronic glomerulonephritis complicating pregnancy; these two patients presented rather marked nitrogen retention (71.2 and 76.4 mg. N.P.N. per 100 c.c.) and were quite toxic. We have obtained similar findings in a number of nonpregnant patients with renal failure and believe that dye retention under such circumstances is dependent upon hepatic functional impairment which may be either "functional" or organic in origin. This problem is under investigation at the present time. However, the absence of any evidence of renal functional impairment in patients with eclampsia is usually of great practical value in differentiating between that condition and glomerulonephritis complicating pregnancy. It should be noted, however, as pointed out by Cantarow and Ricchiuti,<sup>27</sup> that the urea clearance test cannot be relied upon in the estimation of renal functional efficiency during the latter months of gestation. In 2 cases of pyelitis and 1 of carcinoma of the ovary with dye retention, the presence of hepatic disease was not ruled out. The data presented here would appear to suggest that although hepatic functional impairment, as evidenced by bromsulphalein retention, is more consistently present in severe than in mild forms of toxemia of pregnancy, the presence or degree of

dye retention bears no direct relation to the severity of the toxemia. They further demonstrate the observation made elsewhere<sup>1, 28</sup> that dye retention may be present in the absence of hyperbilirubinemia, and vice versa. It is of interest to note that in one case (K. M.) the degree of dye retention dropped from 30 per cent to 7 per cent in twenty-four hours, suggesting that the hepatic functional impairment was perhaps not due entirely to organic or structural changes in the liver.

The data presented in Table IV dealing with the effect of delivery and anesthesia are self-explanatory. One of the three patients receiving no anesthetic (C. H.), with 60 per cent dye retention, showed only 30 per cent retention twenty-four hours following delivery. This patient was suffering with eclampsia, and the apparent rapidity of improvement of liver function suggests, as in the case cited above, that a large part of the hepatic disturbance rests upon a nonorganic basis. Three of the patients who received an anesthetic during labor showed increased dye retention after twenty-four hours; only 1 of these had no dye retention before delivery (L. R.). Of the 4 patients with antepartum dye retention receiving an anesthetic, no increase was noted in 2 cases, slight increase (5 per cent) in 1 (B. T.), and marked increase (60 per cent) in the other (E. K.). This increase was a temporary one, normal findings being obtained in all cases after four days. On the basis of our experience with regard to the effects of anesthesia upon bromsulphalein retention, to be reported later, it would appear that impairment of dye elimination by the liver is more readily produced by anesthetic agents in the pregnant than in the nonpregnant state. They should be employed with particular caution in the presence of evidence of hepatic functional impairment.

#### SUMMARY

1. In a group of 34 normal pregnant women, the serum bilirubin concentration ranged from 0.2 to 1.0 mg. per 100 c.c. Normal results were obtained with the bromsulphalein test in 26 cases; one case showed 20 per cent retention and 7 showed from 5 to 10 per cent retention.

2. Similar studies were performed upon 26 women with toxemia of pregnancy. In 2 cases of eclampsia the serum bilirubin concentration was 1.08 and 0.8 mg. per 100 c.c., and there was bromsulphalein retention of 60 and 20 per cent, respectively. Hyperbilirubinemia was noted in 3 and dye retention (30 per cent) in 2 of 4 patients with a moderate grade of toxemia. Dye retention (from 10 to 30 per cent) was present in 3 of 20 cases of mild toxemia, all of whom presented normal serum bilirubin values.

3. Dye retention (5 per cent) was found in 2 of 4 pregnant women with advanced chronic glomerulonephritis and renal failure, in one with carcinoma of the ovary (5 per cent), and in 2 with pyelitis (5 and 15 per cent, respectively).

4. Studies were made in 15 cases before and twenty-four hours after delivery. An increase in the degree of bromsulphalein retention was noted in 3 patients, all of whom had received an anesthetic at the time of delivery. The serum bilirubin concentration rose in 6 cases, fell in 5, and remained practically unchanged in 4 cases. It appears that impairment of dye elimination is more readily produced by anesthetic agents in the pregnant than in the nonpregnant state.

5. These data suggest that although the serum bilirubin concentration remains within normal limits during normal pregnancy, some degree of hepatic functional impairment is present in a not inconsiderable proportion of cases. The degree of demonstrable impairment of hepatic function in patients with toxemia of pregnancy does not parallel the severity of the toxic manifestations. Studies of hepatic function are, however, of considerable diagnostic value in this connection.

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**Hermstein, A.**: *The Natural Variations in Female Fertility*, *Med. Klin.* 29: 899, 1933.

Some authors contend that there is a physiologic period of sterility in women whereas others deny this. This question can only be answered by determining definitely how long spermatozoa are capable of fertilization, how long ova may remain alive, and the period of ovulation. It is generally conceded that spermatozoa, while they may remain alive for as long as three and a half weeks, are not capable of fertilization for more than forty-eight hours. Ova most likely have a still shorter capability of fertilization. However, the knowledge we have of these germ cells in the human being is very scanty. The period of ovulation in women has not definitely been decided; however, the general consensus of opinion is that ovulation occurs between the fourteenth and sixteenth days. As Ogino points out we should calculate the date of ovulation from the menstrual period which follows and not from the menses which precedes ovulation because ovulation determines the next menstrual period and has nothing to do with the past flow of blood. Ovulation according to Ogino occurs from the twelfth to the sixteenth day before the next menstrual period.

# LABOR IN THE CARDIAC PATIENT\*

## WITH A REPORT OF THE OCCURRENCE OF CORONARY OCCLUSION IN PREGNANCY AND LABOR

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THE association of heart disease and pregnancy is of serious import to the patient. The immediate and remote prognosis is frequently uncertain. The course of the cardiac patient who becomes pregnant must be guided by intelligently planned cooperation between internist and obstetrician.

To approach this problem correctly there must be a complete revision of the prevalent ideas concerning the interrelationship between pregnancy and heart disease. Medical literature is replete with reports and discussions based on the theory that the pregnancy is the primary condition and that the cardiac pathology is the complication. In the light of present knowledge the existing cardiac disease must be regarded as primary and the pregnancy as the complication. Daly and Strouse<sup>3</sup> have stated the problem most accurately: "A woman with organic heart disease who becomes pregnant is immediately treated as a case of pregnancy with medical complications. This position is no longer tenable. The medical side of the complication must become the paramount issue, the pregnancy the complication."

While pregnancy becomes less ominous to the cardiac patient with such a change in attitude, when superimposed it presents certain definite problems. Pregnancy places a mechanical burden upon the heart because of the increase in blood flow, blood volume, and the work of the entire circulatory apparatus. Recent studies show the increase in outflow<sup>14</sup> to be as much as 25 per cent by the fourth month of pregnancy, and 50 to 60 per cent at term. The increase in blood volume<sup>12</sup> is 6 to 9 per cent of the body weight, the actual gain being 400 to 500 gm. The important factors to be considered are, first, this additional work during pregnancy and second, the effect of labor upon the cardiac patient.

*Frequency.*—This study was undertaken to determine the effect of labor upon the cardiac patients who were delivered in the Department of Obstetrics in the Michael Reese Hospital. There were 7,670 patients delivered during the five years ending April 10, 1934; 102 of these, 1.33

\*Read at a meeting of the Chicago Gynecological Society, May 18, 1934.

per cent, had definite cardiac pathology. Reports in the literature as to the frequency of cardiac pathology vary from 4.15 per cent (Stander<sup>10</sup>), 2.7 per cent (Lamb<sup>10</sup>) and 1.11 per cent (Carr and Hamilton<sup>2</sup>) to 0.25 per cent (in the survey made by Sparks<sup>17</sup>), 0.25 per cent (Daly<sup>3</sup>) and 0.16 per cent (FitzGibbon<sup>4</sup>).

In addition 765, or 9.85 per cent, had various types of cardiac murmurs during pregnancy, but showed no signs of heart disease. The frequency of these functional types of murmurs has been variously reported. Lamb<sup>10</sup> found 6.1 per cent; Hamilton and Kellogg,<sup>7, 8</sup> 7.5 per cent. MacKenzie<sup>11</sup> has shown very definitely that this type of murmur in pregnancy is without significance and should have no bearing on the conduct of labor.

Another type of functional disturbance of the heart which is found frequently during pregnancy is the occurrence of extrasystoles. These are usually transient, but occur with increasing frequency in the last trimester of pregnancy. They are of no significance without other evidence of cardiac pathology and practically always disappear after labor.

*Cardiac Pathology.*—Analysis of the types of cardiac pathology found in the 102 patients in this series shows a preponderance of rheumatic heart disease; 86 patients, 85 per cent, had mitral disease. Others have reported this same high incidence of mitral disease of rheumatic origin.<sup>1, 2, 5, 6, 15, 17</sup> In 69 of these, the diagnosis was mitral stenosis and regurgitation. Mitral stenosis alone was found in 11, and mitral regurgitation alone in 6. Two women had, in addition to the mitral disease, definite involvement of the aortic valves, one patient had a partial heart-block due to digitalis and one patient showed a partial heart-block and auricular fibrillation in addition to the mitral disease.

Only six patients in this group showed evidences of decompensation at the time of labor. One patient had congenital syphilis, a marked hyperthyroidism and a lipoid nephrosis. She was delivered of a symphysitis.<sup>13</sup> Another patient had, in addition to her mitral disease, a typical chorea gravidarum. She had a mild decompensation during pregnancy.

Twelve patients showed evidences of myocardosis, two being in association with long-standing, severe hyperthyroidism, two in association with arteriosclerosis, and two secondary to nephritis. Only one of these twelve suffered decompensation during pregnancy or labor. The clinical course of this patient was so unusual that it merits a detailed report.

Mrs. N., forty-five years of age, a gravida vi, para iv, was admitted to the gynecologic service Oct. 10, 1933, in her fourteenth week of pregnancy for therapeutic abortion and sterilization, because of a chronic myocardosis, arteriosclerosis, and hypertension (210/140) complicated by a nephrosclerosis. The husband and one living child being definite syphilitics, the patient was placed on the usual anti-syphilitic treatment in spite of repeated negative Wassermann and Kahn reactions. She was discharged after one week, having refused to permit the pregnancy to be

terminated. She was readmitted when thirty-four weeks pregnant with marked evidences of decompensation in spite of close medical observation in the outpatient department. At this time her systolic pressure was 166. With prolonged rest in bed and appropriate therapy her blood pressure rose to its former level (210/120). On April 2, 1934, while still in the hospital, she developed a coronary occlusion with moderate heart failure. She recovered from this attack and on April 4, 1934, the membranes ruptured spontaneously, following which she had a second coronary occlusion with symptoms less marked than in the initial attack. During this time the pregnancy was ignored, in spite of the fact that she was at term and that the membranes had ruptured spontaneously. Forty hours after the rupture and the second occlusion, labor set in. She was given morphine at fre-

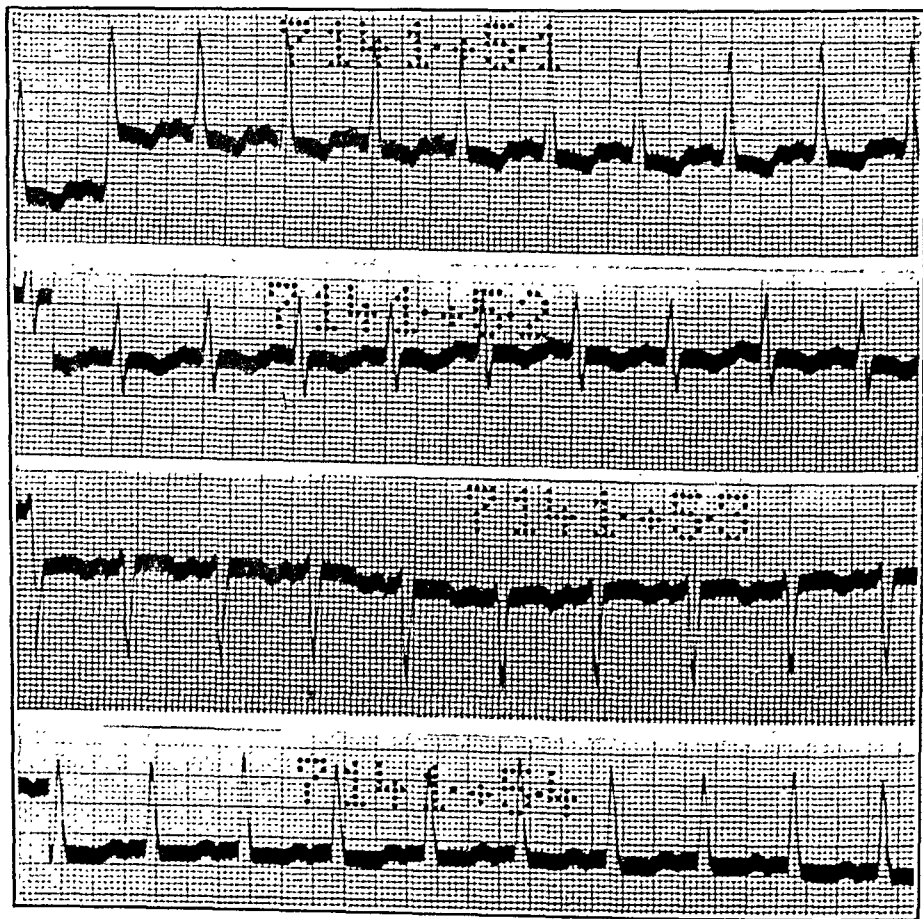


Fig. 1.—Rate 100. P-R interval 0.16 sec. S-T<sub>1,2</sub> negative. T<sub>2</sub> is now definitely inverted. T<sub>3</sub> is flatter. T<sub>4</sub> is much smaller and tends to be diphasic. Sinus tachycardia. Changes since last record strongly suggest a recent coronary occlusion.

quent intervals and after eleven hours of labor, cervical effacement and dilatation being completed, labor was terminated by low forceps extraction to eliminate the second stage. Her immediate convalescence has been entirely uneventful.

As far as can be determined from a search of the literature, the recognition of this occurrence of coronary occlusion in pregnancy or labor is unique.

Other cardiac pathology included myocardosis, 12; with hyperthyroidism 2, arteriosclerosis 2, nephritis 1, auricular fibrillation 1, nephro-

sclerosis and coronary occlusion 1. Congenital heart lesions were found in 3 cases, and auricular fibrillation in 1. None of these had any cardiac embarrassment during pregnancy or labor.

*Parity.*—The clinical course of the cardiac patient during the period subsequent to her last pregnancy should afford an index of her safety in further pregnancies. The fact that a damaged heart will go through pregnancy and labor without symptoms and without any evidence of cardiac embarrassment or failure should not be taken as a criterion for subsequent pregnancies. Scott and Henderson<sup>15</sup> have pointed out the fact that while a patient may stand pregnancy and labor uneventfully as a primipara, she may die some years later of a failure in a second pregnancy. This fact is especially important since the majority of patients suffer from mitral disease of rheumatic origin, a condition which is notoriously progressive.

On the other hand it is of interest to note the fact that many patients with definite rheumatic mitral disease go through repeated pregnancies with apparently no ill effects. It must be assumed that the cardiac pathology in these patients is stationary rather than progressive. It must further be assumed that there was practically no myocardial damage in any of this group since cardiac efficiency is dependent upon the condition of the myocardium rather than upon the valvular lesion. Of the patients in this series 34 were primiparas, 24 were in their second pregnancy, 16 in their third, and 13 in their fourth. Of the remaining 15 patients, 12 suffered from mitral lesions of rheumatic origin; 5 were in their fifth, 2 in their sixth, 2 in their seventh, 2 in their eighth, 2 in their ninth, 1 in her eleventh, and 1 in her seventeenth pregnancy.

It has been shown previously that a large percentage of cardiac patients do not carry to full term, a fact which should be beneficial. In this series 75 patients (74 per cent) carried to term. One patient carried four weeks past her calculated date. Of the remainder, 24 (22 per cent) were delivered between the twenty-eighth and thirty-eighth week of pregnancy. In seven of these labor was induced, the remainder, 16, had spontaneous premature labor.

*Length of labor.*—It has frequently been stated that spontaneous labor is more rapid in the cardiac patient than in the noncardiac. This has been explained by the fact that the increased edema of the soft parts and especially of the cervix tends toward rapid effacement and dilatation and an increased rate in the descent of the fetal head. Labor should be shorter than average in a group of cardiac patients. This is borne out by an analysis of the length of labor in this series. The average length of the first stage of labor in the primiparas was eleven hours and three minutes, and in multiparas was six hours and thirty-five minutes. The average total length of labor for the primiparas was twelve hours and for the multiparas, seven hours and twenty-four minutes.



*Conduct of labor.*—The cardiac patient who becomes pregnant must have careful medical supervision throughout her pregnancy. Such care includes restriction of activity and proper medication as indicated. The all important factor for the cardiac patient whose heart is tottering on the brink of decompensation is the proper restriction of activities and her ability to carry out such enforced rest. Here the social status plays a rôle. The cardiac patient of means can insure the maintenance of her cardiac compensation to a large extent by prolonged rest. The working woman who must continue her household duties is apt to decompensate much more frequently. Scott and Henderson<sup>15</sup> have shown that cardiac failure during pregnancy is twice as frequent among service patients as in a private clientele. In order that the morbidity and mortality in the two groups will be the same, service patients must have available the same opportunity for necessary rest as do the private patients.

Under ideal conditions the cardiac patient will, in the vast majority of instances, begin her labor with cardiac compensation and with the necessary cardiac reserve. These must be maintained throughout the first stage of labor by the adequate use of morphine, sedatives, or various analgesics. The use of morphine still furnishes the best means of insuring rest during labor; morphine also is of inestimable value for resting the damaged heart. Therefore, the liberal use of morphine is doubly indicated for the cardiac patient.

A definite amount of muscular effort is required to complete the second stage of labor spontaneously. It is generally considered that the repeated effort of bearing down is too great a strain to place upon an already diseased heart; hence the admonition in practically every discussion on this subject in the literature that the second stage of labor must be eliminated. In the abstract, this would seem to be correct. Since the amount of muscular work entailed upon the patient in completing the second stage spontaneously is dependent upon a combination of many factors such as multiparity, size of the fetus, pelvic measurements and condition of the soft parts, it would not seem judicious to generalize too completely. As is shown, the majority of the women in this series had short and comparatively easy second stages ending in spontaneous delivery. Only 65 per cent required anesthesia. Five women in this series had multiple pregnancies. These five sets of twins were delivered spontaneously without any great effort on the part of the patient because of the fact that these fetuses were smaller than average.

Of the twenty-six primiparas who were delivered vaginally, 12 had spontaneous deliveries, 11 were terminated by low forceps, 1 by mid-forceps, 1 by version and extraction and 1 by manual aid of a breech presentation. Of the fifty-six multiparas who were delivered vaginally only 9 required low forceps, 1 a version and extraction, and 1 manual aid of a breech presentation.

*Anesthesia.*—As stated above, 35 per cent were allowed to deliver without anesthesia. It has been the experience at the Michael Reese Hospital that ethylene is a perfectly safe anesthetic for the cardiac patient, and is the anesthetic of choice. Of the 65 patients requiring anesthesia, 43 had ethylene, 3 had ethylene and ether, and 7 had ether alone. In these latter the ether was administered by the house staff at a time when no anesthetist was available, only the full-time anesthetists being allowed to administer ethylene. Eleven of the patients were delivered by cesarean section under local anesthesia, and two under spinal anesthesia.

*Third Stage of Labor.*—The third stage of labor carries a small, but very definite risk for the cardiac patient. The more or less sudden decrease in intraabdominal pressure coupled with the lowering of the diaphragm and the abrupt change in the cardiac axis are all factors which can lead to cardiac collapse. This is well illustrated, first, by the case previously reported in detail in which rupture of the membranes was immediately followed by a coronary occlusion, and, second, by one fatality in this series which will be described later. This second patient also showed postmortem evidence of coronary disease.

In an attempt to obviate the sudden disasters which have been reported in the third stage, it has been the routine for many years in the Michael Reese Hospital to place sandbags on the abdomen concurrently with the expulsion of the child. It is worthy of note in this connection that in the two fatalities in this series this routine was not carried out. In the remaining 100 patients there were no accidents in connection with the third stage, and in none was there any break in compensation either during this stage or in the puerperium.

*Cesarean Section.*—Of the 102 patients, 20 were delivered by cesarean section. This is too high an incidence. It should be noted that 9 sections were performed for strictly obstetric indications and were not done because of the cardiac pathology. The indications in 4 of these were acute fulminating toxemia of pregnancy; 2 were done for disproportion after fourteen- and twenty-one-hour tests of labor, respectively; 1 was for chorea gravidarum; 1 was a repeat cesarean section; and 1 for placenta previa.

The cardiac condition was given as the indication in the remaining 11 patients. In 10 of these, sterilization was included as part of the operative procedure. This incidence of over 10 per cent of cesarean section for cardiac disease is still too high. They were considered justifiable because of the fact that sterilization was included in 10. Ideally it would seem better to have the cardiac patient deliver vaginally and return subsequently for sterilization. Experience has shown, however, that the majority of these patients do not return unless they become pregnant again. They will then require therapeutic abortion and sterilization. This latter procedure is less of a physical insult than cesarean section at term. The tendency in recent years at the Michael Reese

Hospital has been away from cesarean section as the ideal method of delivering the cardiac patient. The desire to sterilize the patient should not sway the obstetrician.

*Toxemia.*—There seems to be a definite increased incidence of the toxemias of pregnancy in cardiac patients. This has been previously noted by Corwin<sup>1</sup> and his group, who found an incidence of 19.4 per cent in the cardiac group as compared with 6 per cent in the noncardiac group. In this series 25 of the 102 patients showed definite evidence of toxemia, 24.5 per cent. This includes one patient with chorea gravidarum. During this same period at the Michael Reese Hospital, the incidence of toxemias of pregnancy for all patients was 7 per cent.

*Mortality.*—There were two deaths in this series, a mortality rate of slightly less than 2 per cent.

One patient, a twenty-six-year-old primipara, had a mitral regurgitation of rheumatic origin. She gave no history of decompensation nor was there any evidence of heart failure at any time. Her blood pressure ranged from 120 to 140 during pregnancy and was 150/68 on admission. Labor was induced at term by giving castor oil and stripping of the membranes. The first stage lasted nineteen hours and thirty minutes, during which time she was given two periods of rest by means of morphine. After being in the second stage under ethylene analgesia for fifty minutes the fetal head was still above the level of the ischial spines and the position was L.O.T. At this time a version and extraction was performed under ether anesthesia for failing fetal heart tones. A living female child was obtained. The placenta was delivered spontaneously after eight minutes. Twenty minutes later she became cyanotic and dyspneic with rapid shallow breathing. Her pulse rate jumped to 160 and she soon showed signs of pulmonary edema. Repeated hypodermic injections of morphine and atropine, and intravenous injections of digalen were administered without avail. Death occurred after one hour. Post-mortem examination revealed diseased mitral valves with acute dilatation of the right heart and pulmonary edema. There was also definite sclerosis of the mouths of the coronary arteries and some arteriosclerotic areas in the abdominal aorta. Examination of the uterus failed to show any evidence of injury or hemorrhage due to the version and extraction.

The second patient, a twenty-one-year-old primipara, was first seen on admission to the hospital. There was a loud systolic murmur over the entire precordium, but the heart borders were within normal limits. She was approximately twenty weeks pregnant, had not missed any menstrual periods and had felt fetal motion two weeks before admission. She entered the hospital because of irregular uterine contractions. At this time her blood pressure and urine were normal, and there was slight pitting edema of both ankles. Two hours after hard labor began the membranes ruptured spontaneously and ethylene analgesia was commenced, but after a few whiffs of gas the patient became cyanotic so it was deemed inadvisable to give an anesthesia. Twenty-five minutes later the patient was delivered spontaneously of a two-pound fetus, and three minutes later the placenta was expelled spontaneously. The patient immediately became dyspneic and cyanotic, râles were present in the bases of both lungs, and she commenced to expectorate a frothy pink sputum. Her pulse rate jumped to 140 and in spite of repeated hypodermic injections of morphine and atropine, a venesection with the withdrawal of 200 c.c. of blood, and intravenous digalen, the patient succumbed in two hours. Postmortem examination was refused.

During the five-year period covered by this series, 7,670 patients were delivered at the Michael Reese Hospital with twenty-one maternal deaths, a mortality rate of 0.273 per cent. The mortality due to cardiac pathology, two deaths in 21 total, is 9.52 per cent. Hamilton and Kellogg<sup>7</sup> report a 1 per cent incidence of heart disease, but found that nearly 20 per cent of the maternal deaths were due to the cardiac condition. Carr and Hamilton<sup>2</sup> report a 6.4 per cent, Corwin<sup>1</sup> a 5.8 per cent, Daly<sup>3</sup> a 4.0 per cent and Scott and Henderson<sup>15</sup> a 2.33 per cent mortality rate from heart disease.

*Fetal Mortality.*—Of the 107 babies, three were delivered before viability. There were four fetal deaths (3.76 per cent) among the 104 which were viable. One was a macerated twin, one died of prematurity, one died during the spontaneous delivery of a primipara, and the fourth died during a version and extraction for a prolapsed cord following a bag induction for toxemia.

*Follow-up.*—Of the 100 patients who left the hospital, follow-up data have been obtained on 71. The follow-up period ranged from three months to over four years. All of the thirteen who were followed over four years were well and symptom-free. Of the eleven who were followed over three years, two had complaints referable to their cardiac pathology. Of the sixteen followed over two years, four had symptoms. Thirteen were followed one year; of these two had symptoms, the third patient is critically ill and will probably not survive.

Five were followed six to twelve months; one had symptoms. Of the eight followed three to six months none had symptoms. One, the patient with a coronary occlusion, had a third occlusion one month postpartum and died a week later of cardiac failure. The fifth patient in this group died three weeks after discharge from the hospital. This patient, the second who died in the follow-up group, had evidence of moderately severe decompensation during the latter half of her pregnancy and during labor.

It should be noted that only 11 (15.71 per cent) of these patients had symptoms or gave a history of cardiac embarrassment between the time of delivery and the follow-up. Forty patients have been followed over two years. The low mortality rate, 2.8 per cent, in this group is worthy of note.

#### SUMMARY

The incidence of organic heart disease among the patients delivered at the Michael Reese Hospital during the last five years was 1.33 per cent; an additional 9.85 per cent had functional murmurs; 85 per cent of the cardiac patients had mitral disease of rheumatic origin. The remaining 16 per cent had myocardosis or congenital heart disease. In many women the cardiac pathology of rheumatic origin is stationary rather than progressive; such patients go through repeated pregnancies with no apparent additional disturbances to the circulatory system. Since the

length of labor in many cardiac patients is considerably shortened, and since many deliver prematurely a large percentage is able to tolerate spontaneous delivery; for the remainder the liberal use of morphine during the first stage is essential. In this latter group the second stage should be eliminated under ethylene anesthesia which is well tolerated by the cardiac patient. The frequency of toxemias of pregnancy is increased in women with organic heart disease. Sterilization should not be an indication for cesarean section. The mortality rate in this series was 1.8 per cent in labor, and 2.8 per cent in the delivered group which was followed. Only 15.71 per cent of the 71 patients followed up had symptoms or gave a history of cardiac embarrassment between the time of delivery and the follow-up. Forty patients in this group were followed over two years. A case report of coronary occlusion in pregnancy and labor is made.

### CONCLUSIONS

1. The conduct of labor in the cardiac patient must be individualized.
2. The cardiac pathology demands primary consideration; the pregnancy should always be secondary.
3. Radical obstetrics is unsafe in the presence of decompensation.
4. Neither organic heart disease, nor sterilization, nor the combination should be the indication for cesarean section.
5. The cardiac patient should enter labor well compensated.

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Marmasse, J.: A Case of Spinal Anesthesia, Bull. de la Soc. d'obst et de gynéc., p. 127, February, 1934.

The author reports a case where during labor spinal anesthesia was employed for a forceps delivery. One hour after delivery the anesthetic effects wore off and the patient complained of severe headache and nausea. One hour later she had a typical epileptic convulsion. In discussing such cases, the consensus of opinion at the French Surgical Congress in 1928 was that in cases of spinal anesthesia, meningeal irritation is the cause of loss of consciousness, epileptic convulsions, and psychic disturbances.

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# THE MANAGEMENT OF PREGNANT WOMEN WITH HEART DISEASE\*

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FOR several years there has been endless controversy over the treatment of pregnant women who have associated cardiac disease. The controversial points have included diagnosis; the advisability of marriage and of pregnancy for such patients; the danger such patients encounter should they go through a pregnancy; the relative safety of delivery from below compared to delivery by cesarean section; the value of the sitting posture in delivery; the advisability of terminating pregnancy in the presence of cardiac failure and the effect of pregnancy upon the patient's life expectancy.

## MATERIAL

This paper is based upon a study of the women attending the Prenatal Clinic at Cook County Hospital. Until 1925 this hospital had no prenatal clinic, and the ward service devoted itself to caring for women who came to the hospital in labor or because of some one of the serious complications that require hospitalization during pregnancy. Up to this time our results in the treatment of pregnant women with heart disease was uniformly disappointing, probably because our experience in such cases was limited to those who came to the hospital with acute heart failure. The mortality in other clinics was far better than it was in ours but it was noted that every clinic with a low mortality for such cases had them under observation during pregnancy. In an effort to better our results, we organized a heart clinic for pregnant women. This was a part of the general heart clinic of the hospital in charge of Dr. Don Sutton, and to this special clinic we referred from our prenatal clinic every case in which there were symptoms or findings which might indicate cardiac disease. This practice was continued until the early part of 1933, at which time the clinic was becoming so large that it threatened to overtax our facilities. Since that time we have referred for study in the heart clinic only patients who showed definite evidence of heart disease. The special clinic still has under observation all of the cases which were referred to it except those who have been lost through refusal to cooperate.

During the time we have maintained this special clinic, 19,000 patients have been classified as new patients in the prenatal clinic. From this

\*Read, by invitation, at a meeting of the Chicago Gynecological Society, May 18, 1934.

number 1,350 have been referred to the heart clinic. It appears, therefore, that one patient in fourteen presents something which might lead one to suspect an abnormal heart. Out of this group of 1,350, 126 have been selected as the basis of this report.

#### DIAGNOSIS

These 126 cases comprise only those in which there is no reasonable doubt as to the presence of organic heart disease. The diagnosis of such disease, and the particular type of lesion present has been made or checked by the chief of the general Heart Clinic, Dr. Sutton.

From the original 1,350 cases sent to the cardiac group for study, the great majority have been eliminated for the purpose of this study. Among those which we have left for future investigation are tachycardias without other evidence of cardiac disease; those in which an associated hyperthyroidism might account for the cardiac findings; cases of dyspnea not definitely due to heart complications and arrhythmias without other evidence of heart disease. In short, every case in which the symptoms and findings were insufficient to substantiate the diagnosis of organic heart disease has been held for further study and is not considered in the present group.

We find, therefore, in our whole prenatal clinic, that the incidence of heart disease is 0.66 per cent. This is lower than the general incidence of heart disease, and lower than the incidence of heart disease in pregnancy in most clinics. Thus Munro Kerr<sup>1</sup> reports an incidence of 1.6 per cent in the Glasgow Maternity. Fitzgibbon<sup>2</sup> found 0.16 of 1 per cent of his cases at the Rotunda with a history of decompensation. Burton Hamilton<sup>3</sup> found that 1 per cent of his clinic patients had significant heart disturbance. Our low incidence may be partly due to the fact that for inclusion in this study we have insisted that incontrovertible evidence of organic disease be present.

#### CLASSIFICATION

*The Mitral Group.*—Of the 126 cases, 107 had mitral disease and of these, 61 showed evidence of stenosis. In any group of cardiac patients mitral disease is the most common. Thus Pardee<sup>4</sup> reports 106 with 93 mitral cases, of which 64 showed evidence of stenosis. The age of the patients ranged from fourteen to forty-five. Forty-four came to us in their first pregnancy. Sixty-three had borne children previous to registration in our clinic, the parity running as high as twenty. Twenty-five were colored. Only two had positive Wassermann reactions. Eleven gave a history of previous heart failure. Thirty-seven patients have been under observation for more than five years.

In spite of the fact that this type of lesion falls under the general classification of rheumatic heart disease, only twenty-six gave a history

of rheumatism. Eight had repeated sore throats and two had chorea. Fourteen had scarlet fever. In other words, less than one-third gave a history of any type of rheumatic infection not including scarlet fever. This is a much lower incidence of rheumatic history than that usually recorded. McElroy<sup>6</sup> reports 200 cases from the Royal Free Hospital of London and finds 32 per cent with a definite history of rheumatism or rheumatic fever, and a total of 68 per cent with a history of some type of rheumatic infection. It is possible that the rather low level of intelligence of this group of patients may result in histories that are not accurate.

*The Aortic Group.*—There were twelve cases of aortic disease. Eight patients were twenty years of age or younger. Nine were colored, and five of these had positive Wassermann reactions. Three were diagnosed syphilitic aortitis and in two of these cases we were unable to make a diagnosis on first examination. Two patients gave a history of rheumatism. Half of the group came under observation in their first pregnancy. These twelve patients have been in the clinic for an average time of six years.

*The Combined Group.*—This group includes those in which there was definite evidence of both mitral and aortic lesions. There were seven such patients. All were Wassermann negative and their average time in the clinic has been six years. Only one was under twenty-one years of age, and she was the only one of this group we saw in her first pregnancy. One was colored. Six gave a definite history of rheumatism or rheumatic fever.

#### SYMPTOMS

The most common symptom was dyspnea on exertion. In a group of patients such as ours this may be a very misleading indicator of the seriousness of the heart condition. Dyspnea is complained of by many pregnant women who have perfectly normal hearts. On the other hand, many patients with badly damaged hearts have relatively little dyspnea, and this is especially true of young individuals.

In the mitral group twenty-eight had intermittent dyspnea; twenty-four had moderate dyspnea and in only two was the dyspnea severe. Of the twelve aortic hearts only one had dyspnea as a complaint, but in five of the seven combined lesions it was rather severe.

Edema was the next symptom so far as frequency goes, but again this is a rather common finding in late pregnancy, and does not necessarily indicate myocardial strain. It was noted in twenty-one of the mitral cases, one of the aortics, but in none of the combined lesions.

Chronic cough was present in nineteen of the mitral group, three of the twelve aortics and four of the seven combined lesions. Chest pain occurred in twelve who had mitral, one who had aortic and three who had combined lesions.



Other cardiac symptoms were found in lesser degree, but a remarkable thing is that in a group of 126 badly damaged hearts thirty-five had no symptoms at all. If to this group be added those whose only symptom was mild intermittent dyspnea, 76 or 60 per cent of the whole series were without symptoms.

*Effort.*—We have not classified these patients according to the rules of the American Heart Association for two reasons. The first is that it is the greatest rarity to find an early pregnancy which falls in their Group III, that is cases which have symptoms or signs of heart failure when at rest. The second is that in our treatment we considered them only in relation to their ability to accomplish ordinary tasks. Thus we divided these patients into two classes:

1. Those in whom exertion is not more limited than in other pregnancies of the same duration.
2. Those whose exertion is definitely more limited than the pregnancy could account for.

The statistics relative to symptoms and effort ability refer to findings on first examination. Those cases in which symptoms developed later in pregnancy, or in which symptoms became aggravated will be referred to in considering the management of these patients.

#### MANAGEMENT

Previous to the organization of this clinic, a considerable number of patients with definite evidence of heart failure were sent to the wards in labor. During the time the cardiac clinic for pregnant women has been conducted, a certain number of patients who had not attended the clinic were sent in under similar circumstances. Our inability to care for these patients successfully was very striking. Even those patients not in labor but with advanced heart failure while pregnant resulted in a high percentage of fatalities. Our general plan therefore was to prevent these pregnant cardiacs from developing heart failure. Pardee<sup>4</sup> suggests that "the best treatment of severe cardiac failure is prevention, and this means keeping watch during pregnancy for the appearance of increasing cardiac difficulty, appropriate treatment of the heart as soon as this is discovered and the interruption of pregnancy if the heart fails to respond after two or three weeks." Our previous experience led us to subscribe to this suggestion without reservation, so that we devoted ourselves to prevention rather than treatment.

It became necessary to arrive at some sort of a standard that would enable us to know when these patients began to lose their cardiac reserve or show signs of beginning heart failure. At first we used the exercise test, suggested by Pardee<sup>4</sup> but later we substituted a simpler test, and one that has been quite satisfactory. These patients were all examined at frequent intervals during their pregnancies. So long as they were

able to carry on their ordinary activities without distress, we considered them in no danger. Whenever a patient was unable to do ordinary light housework without dyspnea, or without fatigue; whenever she had difficulty in lying down without more than one pillow under her head; whenever she developed a cough even with no other symptoms, we considered that her myocardium was laboring under strain and she was immediately hospitalized. We were cognizant of the generally accepted physiologic changes of the heart in pregnancy, but in these patients all of whom had damaged hearts, we believed that anything which gave evidence of myocardial distress was sufficient to call for hospitalization. If at routine examination the pulse was over 100 when at rest, or if any irregularity developed, she was hospitalized even if symptoms were absent.

In order to protect the patients from the development of such conditions they were required to spend two hours of each day at complete rest. No other form of treatment was carried out at home. Digitalis was never given during pregnancy while the patient was at home. If in spite of this rest period the patient could not accomplish ordinary household tasks without evidence of cardiac strain she was hospitalized at once.

In the hospital she was treated symptomatically, and whenever the symptoms were of great importance the advice of the physician in charge of the heart clinic was requested. Such a patient was kept in the ward so long as it seemed wise; whenever she could be up and about without distress she was released. Even in the hospital we depended much more on rest, even though secured by sedatives, than on cardiac drugs.

It was our intention always to hospitalize these patients for a few days before they went into labor unless we were convinced of their ability to remain at home safely until labor began. Thus all of the patients with combined lesions were hospitalized before labor, the period of hospitalization ranging from three to twenty-four days. Of the aortic group 40 per cent were hospitalized before labor, and 30 per cent of the mitral group. In addition to this, twenty-four patients were hospitalized at some other time during pregnancy and some of them several times. One para viii was in the hospital for a total of twelve weeks before labor began. She gave a history of heart failure on four previous occasions, and objected to either abortion or sterilization, so that after the fourth month she spent most of her time in the hospital. She was one of the few patients in whom digitalis was necessary over protracted periods.

By this method of hospitalization at the first sign of significant evidence of myocardial stress we were enabled to carry the entire group through pregnancy without the development of alarming symptoms. Two factors undoubtedly contributed to this gratifying result. One was an

efficient social service worker who saw to it that patients returned to the clinic as frequently as we cared to see them. The other was the fact that hospitalization was without cost to the patient so that we were able to send them to the ward whenever and as often as we deemed advisable without considering their financial condition.

Our treatment during labor was likewise extremely simple. Prenatal examination enabled us to make very accurate prediction concerning the presence of cephalopelvic disproportion. Once this factor was eliminated we had to consider only the ability of the heart to withstand the strain of labor. It had been noted by many observers, e.g., Daly,<sup>5</sup> Pardee,<sup>4</sup> Breed and White,<sup>7</sup> Herrick,<sup>8</sup> Corwin et al.,<sup>9</sup> Hay,<sup>10</sup> that cardiaes who begin labor without evidence of heart failure do very well. Inasmuch as our entire group were without marked cardiac distress at the beginning of labor, we felt that uncomplicated labor presented no great hazard. In labor, as well as during pregnancy, no distinction was made between the various types of heart lesion other than as a matter of record. We were interested at all times in the heart's functional ability rather than in its anatomic defects.

Most observers have noted that the first stage of labor, being principally a smooth muscle activity, puts no great strain on the myocardium except that resultant from exhaustion or from mental unrest. Both of these we tried to prevent by sedation. The routine sedative used was morphine gr.  $\frac{1}{4}$  and scopolamine gr.  $\frac{1}{150}$  hypodermically. This was given in primigravidas as soon as the cervix was dilated 3 cm., and in multigravidas as soon as labor definitely had begun. The dose was repeated after four hours if it seemed advisable. In the second stage if progress was rapid, the normal process was not interfered with. If at any time after the cervix was completely dilated progress was slowed or there developed any symptoms of cardiac distress, delivery was accomplished by forceps under ether. It was our experience that these patients when once in labor made satisfactory and frequently very rapid progress.

*Length of Labor.*—In the primigravidas the longest labor was twenty-nine hours, and it was this patient who showed moderate cardiac collapse early in the second stage. The shortest labor was six hours and the average was ten hours and fifty minutes. Those who had borne children previously had an average labor of five hours and forty minutes, the extremes being three hours ten minutes and eight hours fifty minutes.

#### RESULTS

Under this management 126 patients have delivered 189 babies. Two cases aborted spontaneously before five months. Three nonviable premature babies, including one pair of twins, were born. Eleven went

into labor prematurely but after their babies had become viable. Two of these babies failed to survive. One full-term normally delivered infant developed pneumonia and died.

The operative procedures on mothers included one bag induction for associated hypertension and preeclamptic symptoms; one bag induction because the pregnancy was at term. This procedure was not recommended by anyone connected with the antenatal cardiac group. One cesarean section in a multipara done to permit sterilization; 23 low forceps and five midforceps were done in 51 primigravidas; one low forceps and three midforceps were done in 79 multigravidas, and one version and extraction was done on the second twin of a gravida iii. Ether was used in all operative deliveries.

*Maternal Results.*—No patient died during pregnancy or labor. Two patients, one primigravida and one gravida ii showed evidence of acute failure during labor. The gravida ii had been in the ward for several days before labor began because of the gravity of her cardiac condition. Through some error in technic, no one was made aware of the patient's labor pains until the cervix was completely dilated, and there was no first stage analgesia. The patient was rushed to the delivery room, where she at once developed the classical signs of acute heart failure and was delivered ten minutes later in the sitting position. This was the only patient delivered in this position. The primigravida came to the hospital in labor, having refused to accept our advice of hospitalization a week earlier. At the end of a long first stage she showed evidence of moderate cardiac distress, and was delivered by forceps. Both mothers survived. Both babies were born alive, but the baby of the gravida ii died of pneumonia on the seventh day.

One patient died before leaving the hospital. This was a gravida ii whom we had delivered successfully of her first baby two years previously. She was in the ward for observation before labor, and had had no trouble of any sort during pregnancy. At term a bag was inserted to induce labor. No other indication was present for the induction, and it was not recommended by anyone connected with this study. The bag was removed after twenty-four hours and labor started ten hours later. It was an easy four-hour normal labor. On the fifth postpartum day the patient started to run a temperature, which persisted, and gradually increased, until death occurred in the sixth postpartum week. At no time was there definite evidence of pelvic infection, and a diagnosis of malignant endocarditis was made. This was confirmed at autopsy, when most extensive endocardial growths were found, but no other evidence of focal infection.

*Subsequent Results.*—One of these 126 patients died after she left the hospital. This patient was forty-five years old and came to us in her twentieth pregnancy. Six weeks after she left the hospital, she returned in complete cardiac collapse. In ten days she was discharged recovered. Nevertheless she returned at frequent intervals and died on her fifth hospitalization, nine months after delivery. This was not an unexpected death, for most observers agree that the life expectancy of a severely damaged heart is about forty-five years. Reid<sup>11</sup> says, "I feel safe in concluding that as far as these statistics have value they support my clinical impression that women with rheumatic heart disease die before their time not because of marriage and pregnancy but on account of the natural evolution of this disease."

Except for this one case none of these patients was unable to return to the heart clinic for the routine examination which we made six weeks after discharge from the hospital.

Twelve patients have returned to the hospital after delivery because of heart failure. Except for the fatal case just noted, no one returned before five months. These patients have been in the hospital or in a convalescent home from one to five times. Their average age is twenty-eight years. Three have had only one pregnancy. Four have gone on for nine to eighteen months with chronic auricular fibrillation and greatly enlarged livers. One is a para vi now forty-one years old; one a para viii, thirty-six years old; one a para iii, thirty-one years old; and one a para i, twenty-one years old. This we expect, and we expect it to increase. Cohn<sup>12</sup> notes that the annual death rate for rheumatic hearts between twenty and forty years of age is about 3.5 per cent.

Besides the one patient sterilized at cesarean section, ten have been sterilized later, all multiparas. One was sterilized by x-ray. Although she had gone through her three pregnancies with us, and in spite of the fact that we had her in the operating room three times, at no time was her heart in such condition that we felt justified in attempting operative procedures. It is not our attitude that repeated pregnancies result in no increase in heart damage. Neither are we willing to say that the life expectancy of these patients is not diminished by repeated pregnancies. Therefore, we believe that any one of these patients should be sterilized whenever she requests it, and each patient is so informed. The indigent, however, are frequently mentally indolent as well so that while they are not pregnant they do not consider sterilization, and they usually report when the next pregnancy is so well advanced that we consider sterilization only on the most marked indications.

*Comparative Results.*—During the time that this group was under observation, 79 patients with cardiac diseases in pregnancy came to the hospital for treatment or for delivery. All of these came direct to the hospital with congestive heart failure; none of them had attended any clinic previously. Sixty-one were in labor. Twenty-one were in their first pregnancy, 54 were at or near term. Twenty-one of these patients died. Five died undelivered. The others died from ten hours to eleven days after delivery.

No attempt is made to compare the seriousness of the cases which had no prenatal care with those which we had in the clinic. These are cited only to show the value of preventing heart failure. Carr and Hamilton<sup>13</sup> in an excellent report of 500 cases had a very low mortality in the patients who were under control during pregnancy. They also note that in private practice "there have been no deaths so far among the patients that have been under strict medico-obstetric control from early in pregnancy or before pregnancy, if one excepts two patients who died undelivered of diffuse bronchopneumonia. It is equally true that for cases not under strict control the death rate is high."

#### SUMMARY

A series of 126 women with severely damaged hearts has been under observation and strict control during 192 pregnancies.

No patient died during pregnancy or labor.

One died six weeks postpartum from an acute bacterial endocarditis which developed after labor.

One died nine months postpartum at the age of forty-five.

No patient was delivered by cesarean section because of the heart condition.

The most important factor in the care of these patients is the prevention of heart failure. In this effort the cooperation of an internist

and an obstetrician, both of whom have had wide experience in observation of these patients, is invaluable. When heart failure is prevented during pregnancy, disaster during labor or in the postpartum period is a very rare occurrence. It has been our experience that in the absence of obstetric complications necessitating other procedures, delivery *per vaginam* produces results that are extremely gratifying.

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104 SOUTH MICHIGAN AVENUE

#### DISCUSSION

(PAPERS OF DRS. J. E. FITZGERALD, RALPH A. REIS AND L. E. FRANKENTHAL)

DR. LOUIS N. KATZ.—As pregnancy is a normal process for many if not all women, it can only be viewed as a complication of heart disease. Pregnancy and labor are no different from any other type of work imposed upon the cardiac patient. This is the point of view which should be followed by obstetricians and cardiologists.

The blood volume and basal metabolism are increased in pregnancy, particularly in the last months. These changes put an additional demand on the heart. Measurements have shown that vital capacity is decreased in pregnancy, particularly in the last few months. These pulmonary alterations further burden the heart.

There is a real need to examine all patients early in pregnancy when the burden of pregnancy on the heart is not great. I wish to emphasize that there may be difficulty in diagnosing heart disease because many of the clinically accepted signs of heart disease may occur late in pregnancy in the absence of organic heart disease.

One sign of heart failure the clinician often overlooks is the presence of râles in the base of the lungs which is a reliable sign of congestive heart failure.

A patient should be advised against pregnancy, if she has had a recent attack of acute rheumatic fever, if her exercise tolerance is low, if her heart is enlarged or if she has auricular fibrillation.

If the pregnant patient develops symptoms and signs of heart failure in the first three months of pregnancy it is wise to terminate the pregnancy. If heart failure comes on later, it is best to let the patient go on to term.

Labor should be made as easy as possible for the patient. There should be many rest periods during the first stage. In the second stage it would seem that all the assistance that is at all compatible with good practice should be given. After the placenta is expressed, the old-fashioned idea of binding the abdomen is of real value. If the patient has congestive heart failure, it would be better to keep her in a semisupine position throughout labor.

DR. DON C. SUTTON.—I wish to endorse the liberal use of morphine during the first and second stages of labor.

The course of rheumatic heart disease, with some well-known variations, is definite; some patients die of the initial endocarditis; others of severe cardiac

damage at an early age; in many the process becomes quiescent for a period of years, but as a rule, some time between the ages of thirty and forty-five, they succumb.

When the findings of heart disease are so indefinite that a positive diagnosis cannot be made, then the severity of the involvement is so slight that it makes no difference whether or not it is called a normal heart.

The obstetrician deals almost entirely with rheumatic heart disease, and as more than 80 per cent of this group have involvement of the mitral valve, of course most of the cases dealt with are mitral disease, and therefore the most serious.

The girl who has rheumatic heart disease which is not decompensated has the right to marry and perform her main duty of life, the bearing of one or two children, with little worry about materially marring her future if she receives proper prenatal care.

DR. JAMES G. CARR.—My contribution is to present a summary of 23 cases from the records of the Evanston Hospital during the past ten years. Mitral disease was present in eighteen, twice combined with aortic involvement. In three instances the cardiac disease was apparently only a tachycardia in individuals who had formerly had a thyrotoxicosis. One patient sustained a coronary occlusion during her fourth pregnancy; another was regarded as having a dilated heart, for which she was given digitalis during a good part of her pregnancy. In three patients therapeutic abortion was performed early in the pregnancy. In four instances premature labor was induced. Five patients were delivered spontaneously, three of them at term, one at seven and a half months, and another, a para ii, at eight months. Four patients, late primiparas, were delivered with low forceps at term.

Seven patients were subjected to cesarean section. One was in the hospital under observation for six weeks prior to term. A second patient was confined to bed for most of the time prior to the cesarean section. She stood the operation badly and for two or three days was seriously ill. A third patient was subjected to section near term in her second pregnancy, after having gone through a severe collapse at the time of her first labor. Another patient, a woman of thirty-four, was in bed most of the last trimester because of dyspnea and edema when she attempted to be up and around. The cesarean sections were attended with no operative mortality, but one patient who was operated upon at term died within a few weeks of subacute bacterial endocarditis. This patient entered the hospital with fever.

One of the five patients delivered spontaneously was admitted in labor two or three weeks prior to term and easily delivered within a very short time. Her admission temperature was 100°. She had a pronounced collapse, with marked cyanosis and tachycardia, so marked that she was kept in an oxygen tent for many days. Within a few days, positive cultures confirmed the diagnosis of subacute bacterial endocarditis, from which she died six or eight weeks after delivery.

The patient who continues through pregnancy to be free from signs of decompensation may be safely trusted to go into labor. But the patient who shows signs of decompensation should not be allowed to enter or go through labor.

Heart disease is not a statistical problem. It is necessary for the obstetrician and internist together to decide whether a woman, upon the basis of her response to the usual and necessary demands of living during the last months, is able to enter upon the delivery of her baby in a normal way. It is a question of judgment which must be based on experience. No dogmatic rule is acceptable as the basis of our decision as to treatment.

DR. HAROLD H. HILL.—Dr. L. Feldman and I made a study of the electrocardiographic tracings of normal hearts in pregnancy at the University of Illinois. We made the first tracing between the thirty-second and thirty-sixth week, the second

about eight days postpartum and a third at the six weeks' postnatal examination. The third tracing was soon abandoned as there was little or no difference from that of the second reading. Thirty-six women were selected in all. Twenty-one or 58 per cent showed various degrees of left axis deviation, ranging from 13 degrees to 80 degrees rotation in a counterclockwise direction. Variations of under 13 degrees rotation of the electrical axis were not considered significant.

The findings are in accord with the belief that late in pregnancy the heart is in practically a transverse position due to a rising diaphragm and not necessarily to hypertrophy.

DR. WILLIAM C. DANFORTH.—In the first trimester moist râles at the base of the lung associated with other signs of decompensation cause severe anxiety. I have always felt that decompensation in the first trimester calls for termination of the pregnancy. The mere presence of a murmur itself is of very little importance. Men may do severe physical labor with cardiac lesions. The essential thing is whether the heart is doing its work and can continue to do it.

I feel that the majority of women should be delivered vaginally. Where abdominal delivery is used the old classical section should not be performed. It is the poorest way of delivering a patient with cardiac disease, because stormy convalescence may subject the heart to much strain.

The use of morphine during the first stage is important. The length of the first stage is of secondary importance. Of primary importance is that the woman should not be allowed to fatigue herself and should obtain sufficient rest.

Occasionally we hear the recommendation that pregnancy should be terminated prior to term so as to have a smaller baby and an easy labor. This is unwise. It is wiser to allow labor to come on normally because the labor itself is more normal.

I am not as enthusiastic about the use of high forceps as is Dr. Katz, perhaps because I have been on the obstetric firing line.

As far as anesthesia is concerned, I have felt strongly that ether should be used.

With the cooperation of the obstetrician and internist the majority of these patients can be carried through safely, and operative delivery is indicated only in a selected small minority.

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The solid, large cell carcinoma of the ovary, named "Disgerminoma" by Robert Meyer, contains large, round or polyhedral epithelial elements whose protoplasm appears grossly vacuolated. The connective tissue shows hyaline degeneration, and the tumors are richly infiltrated with lymphocytes and many mitotic figures appear. They are rich in cell glycogen, have no hormonal influence on the sex apparatus or the sex function, and appear characteristically in young individuals. As they develop from undifferentiated germ cells they may occur in either sex.

They are associated with 3 types of individuals: (1) pseudohermaphrodites (27 cases have been reported in pseudohermaphrodites); (2) individuals with hypoplastic constitution; (3) normal individuals with a somewhat lowered sex function, i.e. late menarche, frequent sterility.

They are quite malignant and the prognosis is not good, though some excellent results have been reported.

WILLIAM F. MENGERT.



# HEART DISEASE COMPLICATING PREGNANCY

## A CLINICAL STUDY\*

WILLIAM SCHUMAN, M.D., BALTIMORE, MD.

(From the Obstetrical Service of the Sinai Hospital)

IN THE Obstetric Clinic of the Sinai Hospital, a member of the medical staff, Dr. B. J. Cohen, recently was placed in charge of the cardiac patients, studying them in the prenatal clinic and in the ward, intra- and postpartum, with a view to obtaining accurate data on this important medical problem. The series to be discussed in this paper consists of those cases studied prior to his connection with the clinic, with the exception of a few that have come under his observation. The majority of this group received a fairly complete cardiac work-up, having been referred to the cardiac clinic as soon as the cardiopathy was recognized, and were followed by one of two or three cardiologists until the termination of pregnancy, and again after discharge from the hospital. Every case has been carefully followed, and represents the closest cooperation between the cardiac, obstetric, and social service departments, the latter an invaluable cog in the study and treatment of the cardiopath.

The series of cases about to be presented, however small, represents a pretty good cross-section of cardiac clinical material. In all, there are 25 cases of heart disease found at some period of pregnancy or shortly postpartum. They are all ward cases, and therefore do not constitute all the heart cases admitted to the obstetric floors of the Sinai Hospital. The data on private cases being less complete with regard to prenatal histories, it was thought best to eliminate them. However, it can be said with a fair degree of accuracy that the incidence of heart disease among private obstetric patients is considerably less than among the ward cases and, if studied, would prove only half as numerous, a fact which emphasizes the rôle of environmental conditions as an etiologic factor in cardiac disease.

Of the 25 cases, 21 occurred between Jan. 1, 1930 and Nov. 30, 1932, during which period 918 mothers were delivered on the ward service. This gives an incidence of one in every 44 cases, or 2.3 per cent. The 25 patients gave us the opportunity of studying 31 pregnancies. On the basis of the last pregnancy observed, 9 were primiparas, 8 were para ii, 2 were para iii, 1 was para iv, and 5 were more than para iv. Two of the women died as a result of their pregnancy, a maternal mortality of 8 per cent. A third woman died more than six months after delivery with subacute bacterial endocarditis. As far as we are able to determine,

\*Read before the Baltimore Gynecological and Obstetrical Society, November 10, 1933.

22 of the 25 patients are alive today. Only one viable child died (stillborn) out of 18 full-term deliveries. Another full-term child was removed at autopsy from the uterus of its mother who died undelivered.

Eleven individuals gave a definite rheumatic history. The same number had a previous cardiac history, that is, had been treated either in our dispensary or hospital, in some other institution, or by a physician prior to the pregnancy that came under our observation. Fourteen had no previous knowledge of a cardiac condition, and in three cases, cardiac disease was not recognized until labor or the puerperium. In studying the relation of rheumatic history to the severity of the disease, it was noted that of the eleven with positive history, 3 were mild cases, and 8 severe; and of the 14 with no rheumatic history or of doubtful etiology, 6 were mild, and 8 severe. In other words, the chances for a severe lesion are twice as great when the rheumatic history is definite.

The types of lesions as determined by physical signs show a preponderance of the double mitral lesion, 10 of the 25 cases having a mitral stenosis and insufficiency. Next in frequency came mitral stenosis with 5 cases, and third, mitral insufficiency with 5; aortic insufficiency and mitral stenosis accounted for another, combined aortic and mitral insufficiency for still another. One of the two cases that died was diagnosed postmortem as chronic endocarditis of the mitral and aortic valves with cardiac hypertrophy and chronic nephritis. It is interesting to note that 7 of the 10 cases with the double mitral lesion were severe cardiacs, that 4 of the 5 with mitral stenosis alone were severe, and that 3 of the 5 with mitral insufficiency were mild cases. The two cases in which the aortic valve was involved differed markedly in their clinical aspects, one never showed signs of decompensation and delivered spontaneously without embarrassment, the other showed signs of decompensation since early in pregnancy and was sterilized following cesarean section at term.

The plan of treatment in this series was based on the particular needs of each individual case, and not on a group classification similar to those of Pardee, Hamilton and Kellogg, and others. Of the 25 cases, 18 were delivered at term, 6 were interrupted, and 1 died undelivered. Six cesarean sections with sterilization were performed at term, four abdominal hysterotomies and sterilization were done before the viability of the child, and two inductions of abortion were carried out. Ten of the 25, therefore, were sterilized.

Let us consider in some detail the cases treated by cesarean section. There were 6 cases, of which 4 were primiparas and 2 para ii. Four had a definite rheumatic history, 1 indefinite, and 1 negative. They all could be classed as severe cardiacs. Three had combined mitral stenosis and insufficiency, 2 had mitral stenosis, and 1 had aortic insufficiency. Preoperative preparation consisted in absolute rest in bed in hospital for from three to fifty days, and in some cases digitalization. One patient received Lugol's solution. All cases had the classical operation. Anesthetics used were: ether in three cases, local followed by ether in one case, avertin supplemented by local and ether in one case, and spinal anesthesia in one case. The condition of the patient during operation was good in five cases. One patient, who started under local infiltration, went into acute fibrillation at the very onset of the operation, and was finished under ether. Her collapse was ascribed by some to the introduction of novocaine (and adrenalin) into the circulation. The condition immediately following operation was good in four cases, and the patient just described rallied and was in satisfactory condition at the end of the operation. In another case, the pulse rose from 70 to 130 following section. She subsequently died on the seventh day postoperative, and is the only patient in the series that died following delivery. The postoperative complications were: distention and gastric dilatation followed by auricular fibrillation in the woman who died, one pulmonary infarction or pneumonitis which cleared up in three days, and one pelvic infection. The others had a smooth convalescence, and

showed no more discomfort or tachycardia than the usual case of cesarean section. The number of days spent in hospital following operation was from nineteen to twenty-six. There was no fetal mortality in this group.

Considering the group of four cases in which pregnancy was interrupted by abdominal hysterotomy and sterilization, we again note the preponderance of the combined mitral lesion. Three had mitral stenosis and insufficiency, one had mitral stenosis and a possible aortic insufficiency. Periods of gestation were two, two, three, and five months. Three of the four had a positive rheumatic history. All were operated upon under ether anesthesia, and in three the condition during operation and immediately postoperative was good. One patient had a temporary collapse, but quickly rallied.

Induction of abortion was performed in two cases. In the one, the duration of pregnancy was three and one-half months. The cervix was packed with gauze under twilight sleep. She also had a definite rheumatic history, and had a double mitral lesion. She had a moderate tachycardia for eight days postoperative, but subsequently ran a normal course. The second case interrupted was a woman thirty-seven years of age, who had 2 living children and 3 therapeutic abortions. She has had auricular fibrillation for eight years without definite etiology, and with no demonstrable murmur. She was curetted at two months under local infiltration without event.

#### HEART DISEASE AND PUERPERAL MORTALITY

In going over the general maternal mortality in the Sinai Hospital, it was found that heart disease was second among the causes of death in pregnant women. Eclampsia ranks first. Out of a total of 19 obstetric deaths (ward and private) from all causes, 4, or 21 per cent (corrected: 3, or 16 per cent), were attributed to heart disease.

If the figures 10, 15.8, and 16 per cent for heart disease in puerperal deaths found in Reid's, Greenhill's, and my series, respectively, were generally true, this complication of pregnancy would take its place among the leading causes of maternal mortality. The discrepancies between hospital reports and general statistics can only be explained by the fact that the latter include all sources of information, deliveries by midwives and incompetent physicians, as well as unattended cases, among which, I am sure, are countless cases of unrecognized heart disease. DeLee, in his textbook, states that "heart disease in labor is often overlooked." Likewise, I am of the opinion that heart disease in pregnancy exacts a much greater toll of life than is generally believed.

#### CONCLUSIONS

There are several important lessons to be learned from an analysis of this series. First, it makes one more cardiac conscious. Second, it stresses the importance of a careful history from the point of view of etiology of heart disease, especially the rheumatic factor. Third, it emphasizes the necessity of careful auscultation of the heart, for it has been demonstrated unmistakably that mitral stenosis and a combined lesion constitute the most severe types complicating pregnancy.

Most obstetricians confess their inability to time and diagnose accurately heart murmurs. That is excusable, but for an obstetrician or physician to fail to interpret clear facts in the history or to evaluate improperly the symptoms of beginning decompensation is unpardonable.

While the classification by Pardee and others is of great assistance in the study of cases, I am of the opinion that a more simple division into mild and severe cases would be more satisfactory and less difficult. I believe it can be safely said that a mild cardiac can be treated as any other obstetric patient, with the following reservations, limitation of exercise, especially in anticipation of confinement, and shortening of the second stage of labor: The severe cardiac, however, is a problem that must be treated individually. "The decision (whether or not to interrupt pregnancy in any given case) calls for knowledge, large clinical experience, and good judgment." (E. P. Davis.) The parity of the patient, the period of gestation at which she is first seen, her ability to obey instructions, her religion, desire for children, the question of sterilization, and the presence of other complications must all be taken into consideration. If a woman is seen in the early months of pregnancy and has already decompensated, abdominal hysterotomy and sterilization after return of compensation is the treatment of choice. If a patient is seen for the first time after the period of viability with

TABLE I. INCIDENCE

YEAR	DELIVERIES	CARDIACS	INCIDENCE
1930	298	6	1:50
1931	286	5	1:57
1932 (11 mo.)	334	10	1:33
	918	21	1:43.7
Per cent			2.3

TABLE II. RELATION OF HISTORY TO SEVERITY OF HEART DISEASE

	TOTAL	MILD	SEVERE
Pos. rheumatic history	11	3	8
Neg. rheumatic history	14	6	8
	25	9	16

TABLE III. TYPE OF LESION AND RELATION TO SEVERITY

	TOTAL	MILD	SEVERE
Mitral stenosis and insufficiency	10*	3	7
Mitral stenosis	5	1	4
Mitral insufficiency	5	3	2
Aortic insufficiency and mitral stenosis	1	1	0
Aortic insufficiency and mitral insufficiency	1	0	1
Doubtful	1	1	0
Cardiac failure: aortic and mitral lesions, chronic nephritis (autopsy)	1*	0	1
Auricular fibrillation	1		1?
	25	9	16

\*One died.

TABLE IV. TREATMENT (DELIVERY)

	CASES	DEATHS
Spontaneous or low forceps	11	0
Version and breech extraction	1	0
Cesarean section and sterilization	6	1
Abdominal hysterotomy and sterilization	4	0
Induced abortion	2	0
Undelivered	1	1
	25	2

TABLE V. MORTALITY

Maternal, 2 out of 25 (Usual 8 or 10 per cent)	8.0 per cent
Fetal (corrected), 1 out of 18 delivered viable babies	5.5 per cent

TABLE VI. HEART DISEASE AND MISCELLANEOUS MATERNAL DEATHS

Total obstetric deaths	19		
Due to heart disease	4		
Percentage	21.0	Corrected	16.0

a decompensated heart, absolute rest until return of compensation followed by cesarean section and sterilization under ether or local anesthesia gives the best prognosis for mother and child.

Another lesson to be learned from a study of this kind is that the danger is not over with the end of labor. The puerperium may be the most treacherous period, cardiac failure often setting in early or later in the postpartum. This occurred in two of our cases, in both of which heart disease was unrecognized before labor. Both these cases might have been diagnosed antepartum had a second examination of the heart been made in the last prenatal visit. I have adopted and recommend the practice, whenever making a final obstetric examination for the detection of disproportion or malpresentation, also to take an extra minute to examine the heart and base of the lungs; in short, a repetition of the physical examination at term.

## COMMENT

The management of the cardiac in pregnancy is an acid test of her attending physician. While the internist or cardiologist consulted in a given case assumes part of the burden, the ultimate responsibility is the obstetrician's. "In no class of cases is the benefit of intelligent prenatal care and medical observation more strikingly shown than with these patients, and, on the contrary, the absence of this care greatly increases the morbidity and mortality in the presence of this complication." (E. P. Davis.) No better example of unintelligent care is that of a cardiac patient who walked several miles the same day she fell into labor, because, as she said, "the doctor told me to walk every day in the fresh air." Hamilton and Kellogg state that delivery of a patient

in heart failure should be regarded as an indication that some one has blundered. Certainly, Medicine exacts of one of her calling a difficult assignment in the treatment of the pregnant cardiopath.

From the point of view of prophylaxis, we must begin in early life. The adolescent is particularly susceptible to the rheumatic virus, and her health should be carefully supervised, in an effort to prevent rheumatic fever, chorea, tonsillitis, and their complications. The prevention of rheumatic disease by tonsillectomy is quite a debatable question; nevertheless, I would urge the operation routinely in very young children. Better hygiene among the poor is necessary before a reduction in heart disease may be expected. (In one family, two sisters had rheumatic heart disease for which one was sterilized, and a younger sister had Saint Vitus's dance.) The question of marriage in the presence of a cardiac lesion is a subject in itself and need not be discussed here. When one considers the numerous specialists concerned from the beginning to the end of this great problem, the pediatrician, the hygienist, the general practitioner, the internist, the cardiologist, the anesthetist, and the obstetrician, one begins to realize its tremendous scope. It is only by the perfect cooperation between these various branches and by careful research into every aspect of this problem, that we can hope to reduce the great toll of lives sacrificed on the altar of motherhood by reason of a diseased heart.

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#### DISCUSSION

DR. B. J. COHEN.—It is very important that the obstetrician should be cardiac conscious, should take a careful history, and should auscultate thoroughly. Then if the patient should have the slightest anomaly, such as accentuated or roughened sounds, etc., she should be immediately referred to the attending internist or cardiologist. Emphasis should be made on the following important points:

1. *History.*—Patients with a definite history of tonsillitis, chorea or acute rheumatic fever are followed as cardiacs, irrespective of the subjective symptoms.

2. *Anemia.*—Routine blood counts should be done to determine whether or not patient has anemia. One case of mitral stenosis after delivery developed fever. This case was not in our series and was referred for a diagnosis. The patient had a very classical case of subacute bacterial endocarditis, with anemia, splenomegaly,

*Streptococcus viridans* septicemia, etc. Of course death occurred in a few months after delivery. I do feel that this complication may have been prevented, if the patient had been under observation earlier, and pregnancy had been terminated.

3. *Diagnosis and Classification Into Groups.*—I do not feel that a complicated grouping of the cardiac cases is accurate or consistent with the method of treatment. I have formulated a very simple classification. The first group is the so-called undiagnosed or deferred types, which includes cases showing one or more than one of the following findings: (a) slight cardiac enlargement, (b) snapping or roughened or split mitral sounds, (c) accentuated second pulmonic sounds, (d) extra systolic arrhythmia or questionable systolic murmurs with or without subjective symptoms.

The second group comprises all cardiacs in which a definite diagnosis has been made of valvular cardiac disease. It is amazing how frequently we see sudden onset of decompensation with dyspnea, palpitation and tachycardia occur in mitral stenosis cases without any warning, and yet clinically the patient would be regarded as having very good myocardium from routine examination. We therefore regard all valvular cases as severe ones, to be observed closely, so that proper treatment and rest can be instituted at the proper time.

X-rays of heart and electrocardiograms are taken at different intervals throughout the pregnancy. The usefulness of the latter procedure as an aid to diagnosis is still uncertain.

It is important to remember that there are no signs that enable me to diagnose a very early failure, and this alone is a warning to prevent pregnancy whenever possible in a cardiopath, not only to lessen the immediate mortality rate, but also to preserve the myocardium of the patient for the future.

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Moench, G. L.: Variations of the Solubility of the Cervical Mucus in Relation to the Menstrual Cycle, J. Lab. & Clin. Med. 19: 358, 1934.

Moench, in the course of examining sterile couples, has repeated Kurzrock's experiments, using mainly the gross method of immersing the cervical mucus in the semen. Infected cervical mucus was practically not digested by semen (in agreement with Kurzrock) but microscopically was observed penetration of the spermatozoa into the mucus. The degree of penetration seemed to depend on the viscosity of the mucopus or mucus, rather than upon any lytic action of the semen.

Moench favors the idea that the solubility of the cervical mucus varies at different times of the menstrual cycle. It is known that follicular fluid and also the normal secretion of the fallopian tubes and the uterine body dissolve the cervical mucus. In fact, the rubbery consistency of the cervical plug during pregnancy has been explained as being due to the absence of the solvent action of the combined tubouterine secretions. It may be that there is a direct action of the ovary through the folliculin in the blood stream on the cervical mucus, although determinations of circulating female sex hormone were not made, and without such determinations no definite conclusions can be drawn. The few cases presented seem to point to a variation in the properties of the cervical mucus, dependent apparently on ovarian activity.

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EMBRYONAL CARCINOMA OF THE OVARY  
(DISGERMINOMA)\*

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**E**MBRYONAL carcinoma designates a malignant epithelial tumor whose constituent cells present the morphology found in the early developmental stages of the organ in which the growth originates. Both male and female gonads present an embryonal carcinoma with identical gross and microscopic appearance. This surprising occurrence is explained by the following factors:

1. In the first month of asexual embryonal growth, the primitive genital ridge contains sexual and germinal cells.
2. The same sexual and germinal cells comprise the building stones of the ovary and testicle which begin their differentiation between the fourth and sixth weeks of development. In this complex embryologic metamorphosis some of these undifferentiated embryonal cells may be displaced to undergo later neoplastic growth.
3. Arrested gonadal development occurs in both sexes as seen in cryptorchidism and hermaphroditism. It is associated with retention of immature cell types.
4. Both ovary and testicle contain omnipotent sex cells from which teratomas with their irregular admixture of embryonal tissues are supposedly derived.
5. Embryonal cells retain marked growth potentialities and subsequent tumor development frequently occurs.

Since both gonads arise from the same cell prototypes, embryonal carcinoma of similar stamp in ovary and testicle is readily explained. In teratomas, the carcinomatous fraction outgrows and destroys the other tissue components. Striking examples of one-sided teratomas are seen in chorioma testis and struma ovarii.

Although the pathology of embryonal carcinoma of the gonads has long been known, the histogenesis even to date remains problematic. In the testicle Langhans in 1887 described scirrhous and diffuse forms and ascribed their origin to the spermatogenic tubules. Wilms in 1898, demonstrated the teratomatous nature of embryonal carcinoma but traced its origin to the spermatogenic cells in the tubules. In the same year Chevassu described the same tumors as "seminome" deriving it from the spermatoblast. Ewing in 1911 reporting on testicular tumors emphasized the teratoid origin of embryonal carcinoma. In one of his cases minute traces of cartilage were found which "would have been overgrown and eradicated by the rapidly advancing carcinoma." The histologic finding of a lymphoid stroma so frequent in this neoplasm lends additional support to this viewpoint. In the ovary, embryonal carcinoma has for a long time been erroneously reported as large round

\*Read at a meeting of the Brooklyn Gynecological Society, April 6, 1934.



cell sarcoma or endothelioma. The largest series of 48 cases has only recently been reported by Robert Meyer. His terminology of "disgerminoma" would emphasize the origin of this tumor from the primitive germinal cells of the genital ridge. These elements remaining undifferentiated lack the faculty of producing masculine or feminine structures. The high incidence of hermaphroditism clinically encountered with this tumor supports this interpretation.

The gross pathology of ovarian embryonal carcinoma is not distinctive. As a rule the neoplasm is unilateral, round or ovoid in form and of varied size. In the early stages the tumor is firm, gray white, and encapsulated. Later, thrombosis and hemorrhage impart a red or bluish tint. Liquefaction necrosis produces areas of softening. On section the opaque appearance is similar to other solid carcinomas. Microscopically, however, a classical picture is present. The cells are large, round or polygonal in form. The cell cytoplasm is scant and the cell membrane poorly defined. The bulk of the cell is filled with a large, round or oval nucleus, vesicular in character and rich in fine chromatin granules. Mitotic figures are not uncommon. As a rule, the constituent cells are loosely arranged in irregular alveoli demarcated by a fibrillar stroma often infiltrated with lymphocytes. The lymphocytes, however, may be lacking in the scant stroma of the diffuse forms.

Clinically, the subjective complaints are those of other ovarian neoplasms. The onset early in puberty is frequent and distinctive. The incidence of true and false hermaphroditism is strikingly high and was encountered in 27 of the 48 cases reported by Robert Meyer. Women free from this stigma, show genital hypoplasia. Growth of the tumor is rapid and progressive. The prognosis is poor although Robert Meyer reports a favorable response to surgery in the early cases. The literature, however, records many cases with extensive metastases at the onset of clinical symptoms.

The following three cases in the Gynecological Museum of the Long Island College of Medicine emphasize the clinical history and pathologic characters of embryonal carcinoma of the ovary:

CASE 1.—Mrs. M. N., aged fifty-one (Museum No. 27:8:1), was admitted to the Gynecology Service of the Long Island College Hospital on Dec. 17, 1932, complaining of pain in the right lower quadrant and irregular menstruation. The past personal history was essentially negative except for resection of a mesenteric cyst and left salpingo-oophorectomy in 1917. Menstruation began at fourteen, recurred regularly every twenty-eight days and continued for four or five days until the onset of the present illness nine months before admission. At that time the patient noticed menorrhagia which gradually increased in severity. For three months prior to admission the bleeding had been constant and was associated with severe pain in the right lower abdomen. There had been a weight loss of 20 pounds in the past year. Physical examination showed an anemic patient of medium stature. Examination of the head, neck, and thorax was essentially negative. The abdomen was enlarged and asymmetrical; the umbilicus everted. In the right lower quadrant there was found a firm mass evidently arising from the pelvis and extending above Poupart's ligament to the level of the umbilicus. This mass was tender and irreg-

ular. The vaginal examination showed a parous introitus with a relaxed pelvic floor and moderate rectocele. The cervix was firm and fixed. The uterus was displaced to the left by the tumor previously noted on the right side of the abdomen. Examination of the blood and urine showed no abnormalities. The blood pressure was normal. On Jan. 7, 1933, exploratory laparotomy was performed. A tumor mass filled the right side of the pelvis and extended upward to the right hypochondrium. The intestines and omentum were so intimately adherent that their separation caused profuse bleeding. Extirpation was therefore abandoned and the abdomen was closed after the insertion of iodoform packs. On Jan. 11, four days after operation bronchopneumonia developed. This was associated with right suppurative pyelonephritis which caused death of the patient on Feb. 22, 1933, forty-six days following operation.

Partial autopsy limited to reopening of the operative wound was performed the same day. The right pelvic cavity was entirely occupied by a round tumor which



Fig. 1.

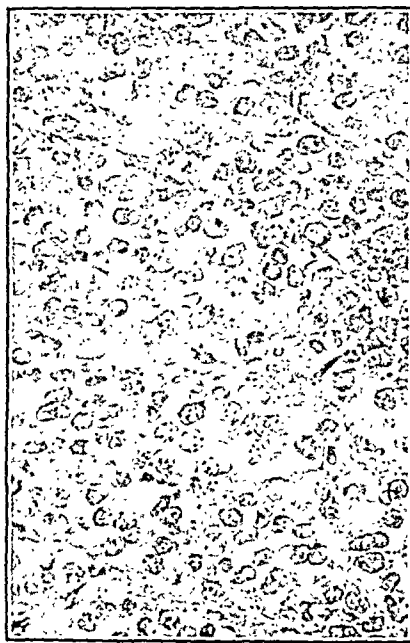


Fig. 2.

Fig. 1.—Case 1. The cut section of the tumor reveals extensive areas of hemorrhage and necrosis. The central and inferior aspects, however, are fairly well preserved. A fibrillar network is just recognizable. The meshes contain opaque tumor tissue.

Fig. 2.—The tumor cells are arranged into irregular alveoli by fine connective tissue trabeculae. The constituent cell is large, almost entirely filled by a large round or oval nucleus which is vesicular in character. There is moderate variation in size, shape, and staining character. (Case 1.)  $\times 350$ .

upon removal measured 19 by 13 by 12 cm. The mesentery, omentum, small and large bowels were firmly fused with the neoplasm. The right kidney pelvis was markedly dilated and filled with fetid greenish yellow pus. The left kidney was normal. The bladder was the seat of a diphtheritic cystitis. The other abdominal viscera presented no striking pathologic changes. The anterior fundal wall of the atrophic uterus contained three small fibromyomas, varying from 1 to 3 cm. in diameter. Microscopically, the characteristic senile changes of the mucosa and muscle were encountered dependent upon subintimal sclerosis of the nutrient arteries. Focally, metastatic collections of epithelial cells were present but only the endometrial

and muscular layers were involved. The left adnexa previously removed were not available for study. The right tube was normal but the parametrium contained microscopic cell rests with characters essentially those to be described in the right ovary.

This organ was converted into a semisolid, lobulated, ovoid tumor measuring as noted above 19 by 13 by 12 cm. The growth direction was intraligamentous. On the anterior aspect of the tumor the tunica had been penetrated by proliferating tumor tissue which was soft, friable, and hemorrhagic. On the posterior aspect the capsule was retained. On cut section the characters were partially obscured by areas of necrosis and interstitial hemorrhage. Thrombosed vessels were prominent. The central and inferior portions of the tumor were well preserved (Fig. 1). A coarsely fibrillar pattern could be differentiated. The meshes were filled with opaque dark gray tumor tissue. Microscopically, multiple sections of the tumor showed large areas of necrosis in which the morphology could not be dif-

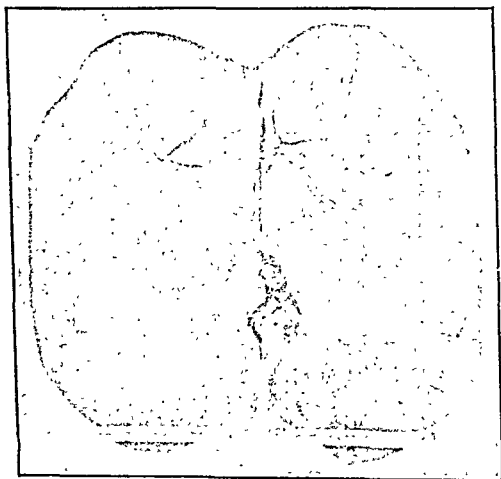


Fig. 3.

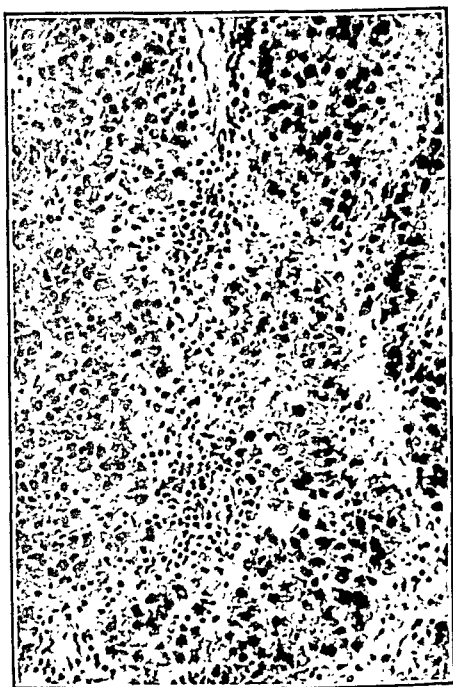


Fig. 4.

Fig. 3.—Case 2. On section the tumor is divided into islands of opaque tissue by well-defined connective tissue trabeculae.

Fig. 4.—The tumor cells are arranged in irregular cords or small alveoli defined by connective tissue septums infiltrated with lymphocytes. The tumor cells are round or oval and almost entirely filled by the nucleus. Lymphoid stroma and the large cell are typical of the lesion. (Case 2.)  $\times 250$ .

ferentiated. In the preserved zones the tunica of the organ was recognizable. The viable tumor cells were grouped into alveoli of irregular size. Focally, however, the growth was diffuse. The constituent cell was large in size, round or oval in form. The cell membrane was faintly defined, the cytoplasm scant and pale staining. The bulk of the cell was filled by a large round or oval faintly staining nucleus of vesicular character (Fig. 2). Variation in size and staining character was not marked. Mitotic figures were observed with only moderate frequency. Occasionally fusion giant cells were encountered. Sections from the anterior aspect of the growth revealed invasion of the capsule with appearance of neoplastic cells on the surface. Anaplastic characters here were more pronounced, the cells showing greater variation in size, shape, and staining character.

CASE 2.—(Museum No. 27:8:3.) This tumor received in 1914 was found catalogued under "large round cell sarcoma." This history is not available. The tumor ovoid in form measured after fixation 14.5 cm. in length, 8.5 cm. in width and 7.5 cm. in thickness. The external surface was smooth and gray white in color. On section the opaque tumor was divided into irregular islands by bands of connective tissue (Fig. 3). Microscopically, broad trabeculae of connective tissue divided the constituent tumor cells into irregular clusters (Fig. 4). Large numbers of lymphocytes were intermingled with the fibroblastic stroma. The tumor cells proper were grouped into long cell columns, irregular alveoli or broad sheaths. Everywhere, however, the cell morphology was identical. The constituent cell was large, round, or oval in form with moderate acidophilic cytoplasm. The bulk of the cell was occupied by a large well-staining nucleus which was round or oval in form. The chromatin content was high but the vesicular character was nevertheless retained. Mitotic figures were numerous. Variation in size, shape, and staining characters were frequent. Focally, coagulation necrosis had occurred. In these areas neutrophils and occasional eosinophiles had appeared in the surrounding stroma.

CASE 3.—Miss M. B., aged thirteen (Museum No. 27:8:4), was admitted to the Long Island College Hospital, June 30, 1931, complaining of enlargement of the abdomen and fever. Menstruation had not as yet appeared. Marked asthenia had been noted for three months. Increase in the size of the abdomen had been present for one month and was associated with progressive respiratory embarrassment. Two weeks later pain appeared. This was confined to the lower abdomen and was cramplike in nature but never intensive. Temperature elevation appeared two days prior to admission. The examination of the head and neck was negative. The thorax showed diminution of the respiratory excursion with occasional râles over both bases. The abdomen was enlarged, distended but generally symmetrical. The abdominal wall was 3 cm. above the level of the costal margin. The lower abdomen contained a tumor evidently originating in the pelvis and reaching 4 cm. above the umbilicus. There was no tenderness or peritoneal rebound. A fluid wave was present. On inspection the external genitalia were normal. The hymen was intact. Rectal examination revealed a tense, cystic mass filling the culdesac. The internal genitalia could not be differentiated. Secondary sex characters had not yet appeared. The urine presented an occasional hyaline cast. Examination of the blood showed hemoglobin 50 per cent, red blood cells 2,750,000, white blood cells 11,400, and neutrophils 85 per cent. The sedimentation time was five minutes. A diagnosis of papillary cyst adenocarcinoma with peritoneal metastases was made. On July 2, 1931, operation was performed under ether anesthesia. The abdominal cavity contained a quart of blood-tinged serous fluid. Lying directly beneath the abdominal wall was a large gray tumor measuring about 15 cm. in diameter. The anterior and lateral surfaces were free. Several loops of small intestine, however, were intimately adherent to the posterior surface. The relation of the tumor to the adnexa could not be clearly established. The omentum was injected and infiltrated with numerous small, friable metastases. Operative removal was abandoned. The abdomen was closed without drainage. Immediately following operation the temperature rose to 104° F. Morbidity persisted for two weeks, the temperature gradually returning to normal. The patient, however, pursued a gradual downhill course and died forty-four days after operation.

Autopsy performed Aug. 15, 1931, was limited to incision through the operative abdominal scar. The abdomen contained abundant serosanguinous fluid. The intestines were displaced upward by a large tumor mass firmly fused with the omentum. The tumor was irregularly lobulated, gray white in color and focally softened and hemorrhagic. The liver showed metastatic growths. The left kidney was enlarged and its upper pole was the seat of a metastatic tumor measuring

about 5 cm. in diameter. Omentum and parietal peritoneum contained metastatic deposits. The uterus was pubescent in type and showed no abnormalities. The left tube was normal, the left ovary elongated and crescent shaped. The right tube was moderately elongated and thin. The right ovary had been converted into a semisolid ovoid tumor mass measuring 18 cm. in length, 12 cm. in width, and 3.5 cm. in its anteroposterior diameter. The tunica of the organ was thickened and preserved except at the superior pole where adhesions of the omentum were noted. On section the tumor was dark gray in color, opaque and presented a distinct fibrous mesh filled with opaque tumor tissue (Fig. 5). In the superior pole a group of four adjacent cysts was encountered. These averaged about 2 cm. in diameter and were filled with opaque thick yellow fluid, probably the end-stage of liquefaction necrosis. In the lower half, opaque gray green areas were noted which represented zones of earlier necrosis. Here, too, liquefaction was encountered. Thrombosed vessels were prominent. Microscopically multiple sections through the



Fig. 5.



Fig. 6.

Fig. 5.—Case 3. Cut section of the tumor shows well-demarcated areas of coagulation and liquefaction necrosis. The central portion is best preserved. A fine fibrillar reticulum is barely recognizable in the opaque homogeneous tumor mass.

Fig. 6.—The tumor cells are arranged in irregular alveoli. The component cells are of relatively large size. The cytoplasm is scant. The bulk of the cell is comprised of a deeply staining nucleus. Variation in size, shape, and staining character is prominent. The supporting stroma is scant. (Case 3.)  $\times 300$ .

viable tumor zones presented similar characteristics. Fine connective tissue septa subdivided the tumor into alveoli of varying size and contour (Fig. 6). Focally diffuse growth was encountered. The constituent cells of the alveoli presented no definite alignment. They were varied in form, generally round or oval, but fusiform types were occasionally present. The cytoplasm was scant in amount, finely granular and stained lightly with eosin. Cell membranes were not prominent. The nuclei were irregular but generally round or oval in form. They were markedly hyperchromatic and stained deeply but the vesicular character was often retained. Moderate numbers of mitotic figures were seen. In many alveoli lymphocytes were prominent and intermingled with carcinoma cells.

# SUMMARY

Three cases of embryonal carcinoma of the ovary are reported. This neoplasm has its exact prototype in the male gonad. Its origin is from embryonal cells of the genital ridge. Teratoid derivation cannot be excluded. Clinically there are no outstanding characteristics but onset early in puberty is frequent. The gross appearance is similar to other solid carcinomas. The histologic picture, however, is distinctive. Large cells with prominent nuclei, supported by a lymphoid stroma produces a classical picture. Diffuse alveolar forms with scant stroma and no lymphocytes have been confused in the older literature with large round cell sarcoma and endothelioma. The prognosis is grave.

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## THE EFFECT OF CIGARET SMOKING DURING PREGNANCY UPON THE FETAL HEART RATE

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THE importance of permeability of the placenta to certain substances and not to others is emphasized by Schlossmann's<sup>16</sup> excellent review of the literature dealing with placental exchange. While we are accustomed to think of the placenta primarily as an organ through which an interchange of nutritive elements from the mother's blood and waste products from the fetal circulation takes place, we may not always appreciate the highly selective nature of this interchange. By reason of this selectivity, the placenta appears to have in addition to functions of nutrition and waste interchange, a protective function. Thus, while a large number of substances pass readily from maternal to fetal circulation in animals, there is evidence that others such as, for instance, bacteriophage, adrenalin, and iron ammonium citrate, do not.

Among those substances about whose transmission across human placental membranes little is known, is nicotine. Because of the recent greatly increased use of tobacco among women, the problem arises as to whether or not the toxic products of the smoke reach and affect the developing fetus if tobacco is used during pregnancy. The work of Tonn,<sup>21</sup> who found nicotine in the milk of mothers whose infants showed evidence of what he believed to be nicotine poisoning, has heightened our interest in the possibility of the prenatal effects of this drug.

If the human placenta is readily permeable to nicotine and other toxic products of tobacco smoke, we might expect to be able to demonstrate them in the umbilical cord blood at birth in those cases where the mother has smoked heavily during the latter months of pregnancy. Sokolov and Lyubovtzeva<sup>19</sup> have shown, however, that animals given large doses of nicotine show a positive blood test for this substance only if the blood is taken within a very short time of the administration of the nicotine. By means of a biologic test for nicotine, consisting of the determination of the effect of the test solution upon the leg muscle of a frog (which is sensitive to 1 part nicotine in 500,000), they were able to demonstrate nicotine in blood taken a longer time after the drug had been administered. Even this very delicate test became negative, however, when the blood was taken a few hours after the nicotine had been injected into the animal. From this work, the difficulties of attempting to determine whether nicotine passes into the fetal circulation by means of an analysis or test of the fetal blood at the time of delivery are apparent. Women do not, as a rule, smoke cigarets during the last few hours before labor. Because of this difficulty, an attempt to determine the presence or absence of nicotine in the fetal blood by measuring any physiologic effect which it might have, has been undertaken. A survey of the literature dealing with the physiologic effects of tobacco convinced us that if the toxic products of tobacco combustion pass into the fetal circulation, some effect upon the rate of the fetal heart might well be expected. Reel<sup>13</sup> has demonstrated the permeability of the human placenta to amyl nitrite by this method.

#### PHYSIOLOGIC EFFECT OF TOBACCO SMOKING UPON THE ADULT HEART

There is considerable difference of opinion as to the harm which may result from the use of tobacco. There is, however, a great deal of evidence that the nicotine absorbed from tobacco smoke does cause variation from normal in the physiology of the cardiovascular system, whether or not these variations are harmful. Lee,<sup>9</sup> Fisher and Berry,<sup>5</sup> and Bates<sup>1</sup> state there is rise in blood pressure which in experienced smokers is gradual and in novices is sharp. Schrumpp-Pierron<sup>17</sup> has observed extrasystoles apparently resulting from excessive use of tobacco. Neuhof<sup>12</sup> has reported a case of sinoauricular block which he believes to be due to tobacco poisoning. Siebert<sup>18</sup> states that the larger number of cardiac neuroses he observed during the war were of nicotine origin. Hett<sup>7</sup> in testing the effects of nicotine in the frog heart, found tachycardia the usual effect after a short period of decreased rate. Clerc and Pezzi<sup>2</sup> found a similar effect on the excised mammalian heart. Parkinson<sup>13</sup> found an increase in pulse rate, from four or five cigarets, of about 9 beats. Fisher and Berry,<sup>5</sup> and Bates<sup>1</sup> also have found a consistent increase in pulse rate immediately following the use of tobacco.

The effect upon the cardiac rate is one upon which most investigators are agreed. Although we have not repeated this work on the effect of tobacco on the adult heart rate in any large series of cases, we have made 22 tests on a total of 5 subjects. In this group, we have found

increases in cardiac rate from 5 to 40 beats as a result of smoking. In these cases, the pulse rate became affected in from thirty seconds to one and one-half minutes after the smoking was begun, and persisted for from five to twelve minutes after the cigaret was finished. The persons upon whom these tests were made were all smokers, using from 2 to 10 cigarets per day. The effect upon the heart rate was not noticeably different in the 2 patients who habitually smoked 10 cigarets daily than it was in the 3 who smoked 4 or less daily.

Whether these effects on cardiac rate and those described by other investigators already mentioned are due to the nicotine or to other toxic products in the tobacco smoke is not positively known.

According to Lehmann,<sup>10</sup> Le Bon,<sup>8</sup> Pictet,<sup>14</sup> Lehmann and Gundermann,<sup>11</sup> Trillat,<sup>22</sup> Droit,<sup>3</sup> Fleig,<sup>6</sup> and others, tobacco smoke contains in addition to nicotine the following poisons: pyridine, thiotetrapyridine, isodipyridine, prussic acid, pyroline, ammonia, collidine, formaldehyde, and carbon monoxide. It is the consensus of opinion of most investigators of the subject, however, that these substances are present in too small quantities to have a demonstrable physiologic effect. Lee,<sup>9</sup> Van Leeuwen,<sup>23</sup> and Lehmann,<sup>10</sup> have proved that the effects of smoking are due practically entirely to the nicotine content of the smoke. They do not feel that other toxic products are present in great enough concentration to cause changes in either heart rate or blood pressure.

#### METHOD OF SECURING FETAL HEART RECORDS

Our observations were made by means of a stop watch and a stethoscope placed upon the maternal abdomen at the point where the fetal heart sound could be heard most clearly. In place of counting the number of beats heard during a given length of time, as is commonly done, we measured the time which elapsed during the counting of ten beats. A table was then constructed by which the elapsed time for ten beats could instantly be converted into the rate per minute of the fetal heart. The count was as follows: as soon as a few beats had been heard to establish the rhythm of the beat, the stop watch was snapped on at the point of maximum intensity of a fetal heart sound. As the watch was snapped on the count was started as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, ending at the point of maximum intensity of the sound on which the count ten was made. An assistant was employed at all times to record the results of the determinations.

We feel that the method is subject to considerably less error than is the fractional minute method in which there is error from the confusion of fractional beats, which sometimes must be dealt with when counting heart beats for a given length of time. Since only ten or twenty beats are counted by our method, any interference with the perception of fetal heart, such as uterine souffle, movement of gas in the intestines, etc., can invalidate only a very short period of the record. By the use of the ten on beat method, the inaccuracies resulting from fatigue and confusion when counting a rapid fetal heart for a minute or half minute are eliminated.

The accuracy of the investigator who made the determinations of fetal heart rate was checked by having him count, and time in a similar manner clicks of a known frequency (from 120 to 180) which were sent through an ordinary telephone headset. During several hundred of these checks, the time recorded for ten of these clicks did not vary more than one-tenth second from the actual elapsed time of ten clicks. A second check was made by having two individuals record the rate of the same fetal heart at the same time. It was found that the difference between the results



of the two investigators was never more than one-tenth second. The limits of accuracy of any individual record was therefore from 1 to 3 beats, according to the rate of the heart. With 6 to 9 samples being taken per minute, the errors tend to become compensated, and the accuracy of the average rate per minute is much higher than that of any individual sample.

#### DISCUSSION OF STATISTICAL TREATMENT OF MATERIAL

To use the statistical method advisedly in a study of this nature, the variables under consideration must satisfy certain conditions. Eb-  
binghaus<sup>4</sup> has criticized the indiscriminate use of the statistical method and gives several criteria for determining whether this method is applicable to the data of a given experimental problem. The first consideration concerns the distribution of the samplings about the mean. Only normal distributions are applicable to this treatment. If it is skewed considerably ordinary statistics will give distorted and unreliable results. Hence a determination of the distribution of the samplings of the heart rate about the mean is not misplaced in this study.

In order to determine the validity of our data, the distribution of the first 2,200 control samplings on the first two patients were plotted. The resulting curves deviated less than the sampling error from the probability curve. The data are therefore applicable to statistical analysis.

The method of procedure of the experiment was as follows: Records of fetal heart during smoking were secured from five subjects. Fetal heart rate samplings were taken for a minimum of five minutes before lighting each cigaret, and for at least fourteen minutes after. Four of the five subjects were habitual cigaret smokers, while the fifth (Subject E) had not smoked previous to undertaking it for our experiment. From this data the mean values of the fetal heart rate for each minute were calculated for each of the 81 records. The average rate for each minute before and after the start of smoking was then calculated and the values plotted in Fig. 1. As is seen in this chart, the maximum effect occurs during the period from the seventh to the twelfth minute following the beginning of the smoke. The effect during the period for each of the five subjects is analyzed in Table I.

The average increase in fetal heart rate after smoking, as shown by the chart, is  $5.0 \pm 0.19$  beats. Since the difference between the rate during the control period

TABLE I. THE EFFECT OF MATERNAL SMOKING ON FETAL HEART RATE

SUBJECT	NUMBER OF RECORDS	FETAL HEART RATE BEFORE SMOKING MEAN $\pm$ PE <sub>M</sub>	FETAL HEART RATE 8-12 MIN. AFTER BEGINNING SMOKING MEAN $\pm$ PE <sub>M</sub>	CHANGE $\pm$ PE <sub>D</sub>
A	32	141.3 $\pm$ 0.23	149.0 $\pm$ 0.27	7.7 $\pm$ 0.35
B	18	144.0 $\pm$ 0.32	151.2 $\pm$ 0.36	7.2 $\pm$ 0.48
C	1	140.5 $\pm$ 0.49	146.5 $\pm$ 1.22	6.0 $\pm$ 1.31
D	20	148.0 $\pm$ 0.24	150.8 $\pm$ 0.22	2.7 $\pm$ 0.33
E	10	145.4 $\pm$ 0.44	140.3 $\pm$ 0.38	5.1 $\pm$ 0.57
Average		144.0 $\pm$ 0.14	149.0 $\pm$ 0.13	5.0 $\pm$ 0.19

and the rate for the five minutes following the cigaret is more than 25 times the probable error of the difference, there is ample statistical evidence for our conclusion that maternal cigaret smoking does increase fetal heart rate.

Of the five subjects studied, Case E consistently showed a decrease in fetal heart rate following smoking, while all of the others showed an increase. This difference, may, of course, be due to any one of a number of things. We have felt that it was most probably due to the fact that the subject had not smoked previous to this experiment and therefore went through the mechanics of smoking very poorly. Unlike the other four, she did not inhale. Her smoking consisted of filling her mouth with smoke and then expelling it as quickly as possible. It is probable that the amount of toxic material absorbed from the smoke under these circumstances was very much less than that in the cases of those who inhaled the smoke and retained it for a much longer period. This explanation is in agreement with the findings of others who have investigated the effect of tobacco on the adult heart rate. Sollmann<sup>20</sup> states that small doses of nicotine cause slowing of the heart while larger

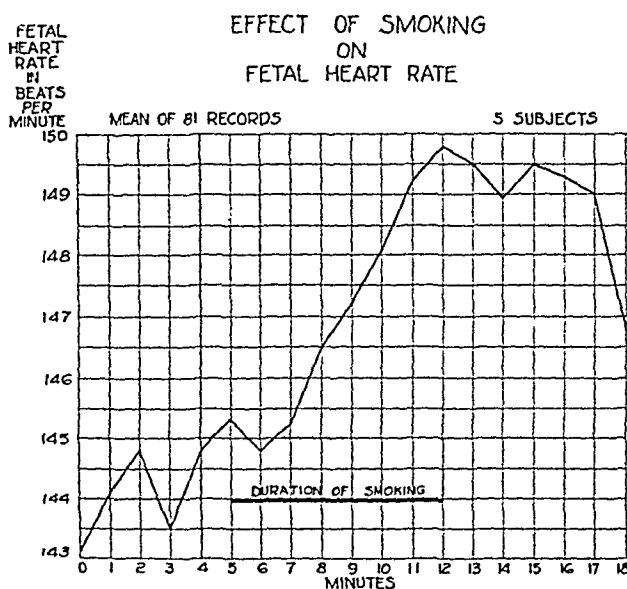


Fig. 1.

doses accelerate it. Parkinson<sup>13</sup> found that experienced tobacco users who inhaled the smoke showed an increase in heart rate, but that those who did not inhale frequently showed no increase and sometimes a decrease in heart rate.

Among the records of the remaining 4 patients, there are scattered instances of individual negative results. While not all 81 of the patients have been analyzed individually in order to make available the mean heart rate before smoking and after smoking for each trial, such data are available for the first 12 trials on Case A. In this series there are two negative results. While the mean of the heart rate before smoking in those 12 trials was  $140.2 \pm 0.20$  beats, the means of the periods before smoking of the two negative trials were  $151.7 \pm 0.77$ , and  $154.0 \pm 0.63$ . It is evident that during the control period for both the negative trials the rate for some reason was more rapid than it was over the period as a whole. This situation would suggest that the fetal heart rate in these patients had been stimulated to an increased rate previous to the beginning trials, and that since the rate had been raised from 11 to 14 beats above its normal, it tended to subside when the effect of the unknown stimulus wore off. The fact that a fresh stimulus (the products of the tobacco

smoke) which would normally increase the rate from 4 to 7 or more beats, came into action at this time, would not be sufficient to maintain or increase the accelerated rate.

### SUMMARY

A study of fetal heart rate before and after maternal smoking has been made a total of 81 times on 5 patients. The object of the study has been to determine the effect, if any, of maternal smoking on fetal heart rate. It was felt that if fetal heart rate was altered by maternal smoking, this change would indicate that the toxic products of tobacco smoke do pass through the human placenta and enter the fetal circulation. The results of the observations are as follows:

1. The average fetal heart rate for five minutes before smoking was  $144.0 \pm 0.14$ . The average fetal heart rate for the eighth to the twelfth minute after a cigaret was lighted and smoking begun, was  $149.0 \pm 0.13$ . The average increase in the rate was  $5.0 \pm 0.19$  beats. Since the difference in rates before and after smoking is more than 25 times the probable error of the difference, the effect of smoking is actual.

2. Of the 5 patients, 4 showed an increase in fetal heart rate after smoking, while the fifth showed a decrease. The 4 showing increases were habitual smokers who inhaled the smoke. The patient showing decrease had never smoked before, did not inhale, and expelled the smoke from her mouth as quickly as possible.

3. There were occasional negative trials in each of the 4 patients showing increase. These occurred for the most part at times when the fetal heart rate during the control period was above its average.

### CONCLUSIONS

1. There is a definite and real effect of maternal smoking upon the rate of the fetal heart.

2. This increase appears to be due to the passage of the toxic products of tobacco smoke into the fetal circulation where they affect the fetal heart rate in the same way that adult heart rate is affected.

3. Since the toxic effects of tobacco upon young children and of nicotine contained in mothers' milk on nurslings have been reported, a careful study of the newborn offspring of mothers who smoke heavily during pregnancy is indicated. Evidence of injurious effects of smoking during pregnancy may be overlooked.

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## OVARIAN FOLLICULAR HORMONE EFFECTS ON THE OVARIES

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**B**ENEFICIAL results have been reported by Lewis, 1933,<sup>1</sup> from therapeutic use of ovarian follicular hormone (theelin, amniotin) in the treatment of gonorrheal vaginitis in children. He observed the effects of the treatment during the course of the infection by frequent examination of the vagina with the usual smear technic, and studied the reaction of the vaginal epithelium to this hormone in histologic sections of small pieces removed at biopsy.

The reasoning which prompted the use of this treatment was decidedly logical. During the last few months of gestation rapid growth occurs in the genital tract of the female fetus. This has been attributed to the large amount of theelin (or theelol) in the blood of the fetus. Increasing amounts have been demonstrated in the placenta, maternal blood, and urine as gestation progresses. Positive tests for this hormone have been obtained from umbilical cords at term and from cord blood. Therefore, the genital tract of the fetus is subjected to an extremely high concentration of this female sex hormone. During the first month or two of postnatal life the genital tract retrogresses, particularly the uterus, which decreases in size. It is known that after parturition theelin rapidly disappears from the blood of the mother. The rate of excretion in the urine also rapidly declines, amounts being too small to detect on the third or fourth day after delivery. There can be little doubt that separation of the fetus from the placenta at birth ushers in a period of relative theelin deficiency in the blood of the newborn. This results in a withdrawal of the genital growth stimulus, which is followed by a period of involution in both vagina and uterus. This question is reviewed with citations to the literature in Chapter IX, *Sex and Internal Secretions* (Allen, 1932).<sup>2</sup>

It seems logical that at such a time the vagina may be more susceptible to infection by gonococcus than if its tissues were in a well-sustained phase of physiologic activity. It has been adequately demonstrated in

several species of mammals that the ovarian follicular hormone induces the growth, which thickens the vaginal epithelium, and stimulates development of the glands of the uterus, both fundus and cervix. Therefore, the therapeutic use of theelin in infants and young girls should bring these organs into a phase of growth and heightened function and enable them to better combat a gonorrheal infection.

The removal of small pieces of vaginal epithelium at occasional biopsies during the course of hormone treatment of children has demonstrated that this is what actually happens (Lewis, 1933).<sup>1</sup> With the rapid growth of the vaginal wall there is a disappearance of gonococci from the vaginal smears.

One criticism leveled against this therapy, however, was that it might have a harmful effect upon the ovaries, which might result in decreased function during later life. Several investigators have reported marked inhibition of growth of ovaries of rats following the injection of ovarian follicular hormone (Doisy, Curtis and Collier, 1931;<sup>2</sup> Leonard, Meyer and Hisaw, 1931;<sup>4</sup> Katzmman, 1932<sup>5</sup>). Before extensive use of theelin in children the possibility of injury to the ovaries should be tested in young primates. Therefore, a series of experiments with monkeys was planned in which the doses injected were proportionate to those used by Lewis in his patients. These experiments have been continued for periods considered to be adequate for the treatment of gonorrheal vaginitis in infants and young girls.

#### EXPERIMENTAL PROCEDURE

Six immature female monkeys (*Macacus rhesus*) were used, three for experimental purposes, and three at the same stage of development for controls. They ranged in body weight from 2,085 to 2,425 gm.; the smallest was 15.5 months old and the largest probably slightly over two years of age.

Laparotomies were performed before beginning injections, and measurements of the ovaries and uterus made as additional control observations. Then subcutaneous injections of follicular hormone were begun. To insure maintenance of the hormone level, two injections were given daily. The treatment was continued for twenty-eight days in each of two monkeys, and for thirty-nine days in a third. In the first two animals injections were begun with doses of 20 rat units daily, gradually increased to 70 rat units on the twenty-first day, and continued at this level until the twenty-eighth day; the total dosage exceeding 1,390 rat units. In the third monkey a beginning daily dose of 35 rat units was increased by stages to 80 rat units on the thirtieth day and continued at this level through the thirty-ninth day; the total dosage exceeding 2,382 rat units. The hormone used was "Amniotin," assayed at 50 rat units per c.c.\*

The effects of the injected hormone were followed by observations of the reddening and swelling of the "sexual skin" around the external genital organs, on the back of the thighs and base of the tail, as previously described (Allen, 1927<sup>6</sup> and 1928<sup>7</sup>). The question of excretion of hormone from possible overdoses was stud-

\*Grateful acknowledgment is made to E. R. Squibb & Sons and Dr. John F. Anderson for supplying this preparation.

ied by testing extracts of overnight samples of urine for theelin content. Thirty-three tests were made in ovariectomized rats. Extracts of several samples of feces ranging in amounts from 10 to 25 gm. were also tested.

At the end of the injection treatment each animal was operated upon and the ovaries and uterus measured for comparison with the control measurements of the same organs. Then the right ovary and uterine tube were removed for study of possible immediate harmful effects. The left ovary and tube and the uterus were left intact for recovery periods of thirty days and removed later at autopsy for histologic study, along with other organs and glands of internal secretion.

## OBSERVATIONS

At the beginning of the experiment the "sexual skin" was pale and not swollen, for the monkeys were sexually immature. The uteri were small and anemic. The ovaries were small, pearly white in color, and contained no superficial follicles large enough to be visible from the surface (see Table I).

TABLE I. BODY WEIGHTS (IN GRAMS) AND MEASUREMENTS (IN MILLIMETERS) OF UTERI AND OVARIES (1) BEFORE AND (2) AFTER INJECTIONS, AND (3) AFTER A MONTH'S RECOVERY PERIOD

MONKEY	DATE 1933	BODY WEIGHTS	UTERUS	RIGHT OVARY	LEFT OVARY
C (1)	4-12	2,085	8.5 × 3	6 × 4.5 × 3	6 × 4.5 × 3
C (2)	5-15	2,255	16 × 11	5 × 4.5 × 2.5	5 × 4.5 × 2.5
C (3)	6-14	2,410	12.5 × 6		5.5 × 4.5 × 3
NC (1)	4-12	2,425	10 × 4.5	8 × 5.5 × 4	9 × 5 × 4
NC (2)	5-15	2,655	15 × 14	8 × 4.5 × 4	8 × 4.5 × 4
NC (3)	6-14	2,780	11.5 × 7		8.5 × 4 × 4
SM (1)	4-26	2,300	7.5 × 3	7.5 × 3.5 × 2.5	7.5 × 3.5 × 2.5
SM (2)	6- 5		17 × 12	7.5 × 3 × 2.5	7.5 × 3 × 2.5
SM (3)	7- 8	2,740	12 × 6		8 × 4.5 × 2

Effects of the injected hormone were first evident in reddening and swelling of the "sexual skin." As injections were continued these secondary sex characteristics were intensified. Toward the end of the experiment the areas affected averaged 13 by 10 by 4 cm. Within from seven to ten days after cessation of injections the color had faded and the swelling regressed to control conditions. Judging from previous experience with this "sexual skin" reaction, an effective level of hormone concentration was maintained during the course of the experiment.

A second indication of maintenance of a continuous high level of hormone was the decided increase in size of the uteri during the course of injections. A comparison of the first and second measurements of the uterus of each animal in Table I shows an average increase of 7 by 9 mm. in anteroposterior and lateral diameters at the uterotubal junction. In monkeys C and NC these increases were obtained in twenty-eight days and in monkey SM in thirty-nine days.

Thirty-one of the 33 analyses of overnight samples of urine were negative and two were positive. No positive results were obtained from tests of feces. Therefore, the matter of injection of more than threshold doses need not be considered.

Immediately after cessation of injections one ovary and tube were removed from each animal, other genital organs being left intact for an interval of thirty days for recovery from hormone effects. Measurements of the uteri after the recovery period showed much involution, but after thirty days without ovarian hormone influence, other than that from the single immature ovary, the uteri were larger than at the beginning of the experiment.

Measurements of the ovaries (Table I) before and immediately after the injection treatment showed a slight decrease in size after hormone treatment. After recovery periods of thirty days following cessation of injections, the left ovaries in two monkeys had not regained their full control size. In the third monkey (SM) there was a slight increase over the control measurement. Some compensatory hypertrophy of the second ovary might have been expected after removal of the first, but it is probable that it would not be great until the approach of sexual maturity. That injected animals were still decidedly immature was shown by rapid involution of "sexual skin" phenomena and decreased size of the uterus during the thirty-day period following cessation of injections.

The ovaries were sectioned serially and compared with the controls in a further search for possible harmful effects. The first impression to be noted was that growth of follicles with antra (large) had not progressed in the ovaries as far in injected animals as in those of the controls. There were still present, however, normal follicles of all stages of development typical for immature ovaries. The supply of small cortical follicles was equally plentiful in control and experimental animals.

To analyze more thoroughly the follicular content of these ovaries, a census was taken of normal and atretic follicles. This census is summarized in Table II. It includes as a first class the larger normal follicles in which secretion of liquor folliculi had progressed to the point of formation of definite antra. Included in a second class were small follicles in which ova were surrounded by two or more lay-

TABLE II. INCIDENCE OF NORMAL AND ATRETIC FOLLICLES IN OVARIES OF MONKEYS AFTER INJECTIONS OF OVARIAN HORMONE (AMNIOTIN) AND AFTER THIRTY-DAY RECOVERY PERIODS

MONKEYS	OVARY	TYPES OF FOLLICLES			
		NORMAL		ATRETIC	
		LARGE	SMALL	LARGE	SMALL
Control					
Y <sub>1</sub>	Right	24	121	10	85
12	Right	22	188	4	82
13	Right	10	187	35	79
Experimental					
C	Right	6	49	2	95
	Left	20	54	9	109
NC	Right	30	257	29	282
	Left	52	170	25	306
SM	Right	17	80	8	64
	Left	16	121	8	78

ers of follicle cells, but in which secretion of liquor folliculi had not begun. Atretic follicles were similarly classified. The three control animals appear first. The right and left ovaries of the experimental animals should be considered separately. The right ovary in each case was removed immediately after the series of injections of follicular hormone, the left remained in the animal for a recovery period of thirty days.

It seems clear from a consideration of these data that no serious damage has been done to these ovaries as regards the number of normal follicles present. The proportion of normal to atretic follicles shows little significant variation when the two ovaries of each injected animal are compared. When the injected animals are compared with the controls there seems to be at least a temporary increase of follicular atresia.

This statement, of course, would apply only to the dosage given over the intervals covered by this experiment. There were abundant stocks of small follicles through the cortical zones of ovaries of injected animals. The only definite effect which can be discovered histologically was possible interference with the growth of the larger follicles, which would account for the slight decrease in size of the ovaries immediately after the hormone treatment.

#### SUMMARY AND CONCLUSIONS

1. Injections of ovarian follicular hormone (amniotin), in doses ranging from 1,265 to 1,390 R. U. over periods of twenty-eight and thirty-nine days, were made into immature monkeys. That this hormone treatment was effective was shown by the reddening and swelling of the "sexual skin" and by increase in size of the uterus.

2. Ovaries were studied for possible harmful effects from this treatment. The first ovary in each animal was removed immediately after a series of injections, the second ovary after a thirty-day recovery period. There was a slight decrease in size of the ovaries removed immediately after the period of injections. A month later the second ovary compared favorably with its control size (some compensatory hypertrophy may have been operative during the recovery period). Decrease in size was due to a smaller number of the largest follicles. A census of normal and atretic follicles in experimental and control animals indicated a slight increase in follicular atresia. There were present in ovaries of injected animals many small cortical follicles and comparable numbers of medium-sized normal follicles in which secretion of liquor folliculi had begun.

3. Therefore, as far as can be ascertained histologically, there seems to be little damage to the ovaries, which would be more than temporary, from injections of follicular hormone (amniotin) in the dosage and over the intervals used in these experiments. The therapeutic use of comparable doses of this hormone in children may be prescribed without fear of harmful results upon ovaries.

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# THE VALUE OF IRRADIATION IN THE TREATMENT OF OVARIAN CARCINOMA\*

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IN 1927, Drs. Keene, Pancoast and Pendergrass reported the results obtained from irradiation therapy in 24 cases of inoperable carcinoma of the ovary.† They reached the following conclusions:

1. It is impossible to predict what the effect of irradiation will be on any given patient. This effect will be determined by the first series of treatments; should no benefit be derived, further irradiation is usually a futile procedure.
2. In case of more or less generalized carcinomatosis, in which the primary growth has not been removed, little can be expected from treatment.
3. A decidedly more hopeful outlook, so far as relief from symptoms is concerned, can be anticipated when the primary growth has been removed.

The present study of the results obtained from the postoperative treatment of 38 additional cases confirms these conclusions, except that with the improvement of technic and equipment the prognosis is more favorable for palliation and for the prolongation of life.

This analysis showed that the histologic type of carcinoma is of no value in determining what the effects of roentgen therapy will be. On the other hand, the extension of the growth proved to be of definite prognostic value, and for this reason the patients have been divided into three groups, based upon the degree of involvement at the time of operation (Table I). In the first group, consisting of six patients, complete removal of the affected organ was possible and no visible evidence of the malignancy remained. In the presence of unilateral ovarian carcinoma, the uterus and the opposite ovary should be removed, despite the absence of macroscopic or even frozen section evidence of contralateral involvement.

The second group includes 19 patients from whom the primary growth was removed, but peritoneal metastases were present. The original tumor should be removed when possible, for even in the presence of transplants, this procedure greatly enhances the effect of postoperative irradiation. Frequently the operation alone will be followed by temporary symptom-

\*Read at a meeting of the Obstetrical Society of Philadelphia, May 3, 1934.

†The Value of Irradiation in the Treatment of Inoperable Carcinoma of the Ovary. J. A. M. A. 89: 1053, 1927.

atic improvement and retardation of the malignant process, but more prolonged palliation occurs when roentgen therapy is preceded by surgical removal.

TABLE I. TABULATION ACCORDING TO THE EXTENT OF GROWTH

<i>Patients receiving irradiation</i>		38
Group I.	Entire malignant process apparently removed	6
Group II.	Primary growth removed with transplants remaining	19
Group III.	Generalized peritoneal involvement	13
<i>Patients operated upon only</i>		51
Group I.	Entire malignant process apparently removed	27
Group II.	Primary growth removed with transplants remaining	15
Group III.	Generalized peritoneal involvement	9

The third group, numbering 13 cases, is those with generalized carcinomatosis, in whom it was impossible to do more than an exploratory laparotomy and drainage of the ascites. It is our policy to advise abdominal incision under local anesthesia in such cases, for this affords the safest means of removing ascitic fluid and permits the collection of tissue for microscopic study. Occasionally, removal of the primary growth is unexpectedly possible, thereby increasing the chances of favorable response to irradiation. Furthermore, other pelvic tumors may so closely simulate extensive ovarian carcinoma that exploration is necessary for accurate diagnosis.

For comparison we have included 51 patients who were operated upon in the Gynecological Clinic for ovarian carcinoma but who were not given postoperative irradiation.\*

The length of life after operation offers the most definite basis for comparing the results obtained in the treated and untreated groups. Of the 38 patients who received roentgen therapy, 21 are now dead and 90 per cent of these lived less than two years following the operation (Table II). All the deaths were in Groups II and III. Of the patients who were not given roentgen therapy, 25 are now dead and 89 per cent of these succumbed in less than two years. Since approximately 90 per cent of the deaths in both groups occurred in less than two years after operation, we have analyzed the treated and untreated patients by using the two-year standard of salvage in addition to the usual five-year standard (Table III).

In Group I, of the four patients who received roentgen treatment, all are living, while 15 per cent of the untreated patients died within two years. This suggests the value of roentgen therapy as a prophylactic measure following apparent complete removal of the malignant disease.

\*We are indebted to Dr. Douglas P. Murphy for the use of his follow-up data upon these patients.

In the other groups, the results of irradiation are more definite. Fourteen patients in Group II were treated and four (29 per cent) are alive after two years, while in the untreated cases only two (13 per cent) of 15 patients survived. With generalized carcinomatosis, 25 per cent of the treated patients are alive after two years, in contrast to 11 per cent of those not treated. Finally by combining Groups II and III, we find that 22 per cent of those treated and only 12 per cent of those not treated lived two years or more after operation.

TABLE II. DURATION OF LIFE OF DEAD PATIENTS

	NUMBER OF PATIENTS	SIX MONTHS TO TWO YEARS	TWO TO THREE YEARS	THREE TO FOUR YEARS
<i>Patients Receiving Irradiation</i>				
Group I	0	0	0	0
Group II	12	10	1	1
Group III	9	9	0	0
	21	19 (90%)	1	1
<i>Cases Operated Upon Only</i>				
Group I	4	3	1	0
Group II	13	13	0	0
Group III	8	6	2	0
	25	22 (89%)	3	0

TABLE III. TWO-YEAR SALVAGE

	GROUP I		GROUP II		GROUP III	
	TREATED 4 PATIENTS	UNTREATED 27 PATIENTS	TREATED 14 PATIENTS	UNTREATED 15 PATIENTS	TREATED 8 PATIENTS	UNTREATED 9 PATIENTS
Alive	4 (100%)	23 (85%)	4 (29%)	2 (13%)	2 (25%)	1 (11%)
Dead	0	4 (15%)	10 (71%)	13 (87%)	6 (75%)	8 (89%)

The five-year salvage is summarized in Table IV. While the greatest prolongation of life follows the use of roentgen therapy in all three groups, it is most significant in Group II, where 43 per cent of the treated patients are alive after five years as against 13 per cent of those not treated. While the number of patients in this study is too small to offer conclusive proof, the results suggest that roentgen therapy does aid in prolonging life.

A comparison of our figures and those reported by Drs. Keene, Pancoast, and Pendergrass shows that improvement in equipment and technique has been followed by better results. Of the 18 patients in Group II which they surveyed, none lived five years, while in the present series a five-year salvage was obtained in three out of seven cases. In Group III none of their patients lived more than one year and in this series, 2 out of 6 patients lived more than two years.

Some may question the wisdom of prolonging the existence of these patients, but if they can be made more comfortable at the same time, there can be no doubt of its justification. That relief of the distressing

symptoms produced by extensive ovarian malignancy frequently follows irradiation is shown in Table V. Twenty patients had severe pain and in 60 per cent of these the pain was definitely lessened or en-

TABLE IV. FIVE-YEAR SALVAGE

	GROUP I		GROUP II		GROUP III	
	TREATED 1 PATIENT	UNTREATED 27 PATIENTS	TREATED 7 PATIENTS	UNTREATED 15 PATIENTS	TREATED 6 PATIENTS	UNTREATED 9 PATIENTS
Alive	1 (100%)	23 (85%)	3 (43%)	2 (13%)	1 (17%)	1 (11%)
Dead	0	4 (15%)	4 (57%)	13 (87%)	5 (83%)	8 (89%)

TABLE V. THE RELIEF OF SYMPTOMS

	PRESENT	RELIEF FOLLOWING IRRADIATION
Pain	20	12 (60%)
Ascites	22	8 (36%)
Masses	32	10 (31%)

tirely relieved. Ascites was present in 22 and in 36 per cent its re-accumulation was prevented or retarded. Of the 32 patients who had palpable abdominal masses, reduction in the size of the tumor occurred in 31 per cent and in a few they disappeared. In several instances the masses and ascites recurred at varying intervals following the cessation of treatment, and became less responsive to each successive series until eventually the patient succumbed. We are convinced of the palliative value of roentgen therapy. Although the relief is often temporary it is sufficient to warrant treatment even in the presence of advanced ovarian carcinoma.

Forty per cent of the patients in this series experienced severe irradiation sickness, which constitutes the chief objection to this form of treatment. The reactions were especially prone to occur in Group III in which one-half of the patients became extremely ill during the treatments, while one-seventh of those in the other two groups were similarly affected.

It is impossible to predict the effect of roentgen therapy upon a given patient. While the extent of the growth is the best guide to prognosis, it is not infallible as is shown by the following case. Mrs. E. B., aged thirty-seven, was operated upon by Dr. F. E. Keene, on April 6, 1929, for extensive ovarian carcinoma. Microscopic examination revealed adenocarcinoma. A huge quantity of ascites was evacuated and the carcinomatous process was found to be so extensive that removal of the primary growth was impossible. The peritoneum was studded with metastatic nodules. Deep roentgen therapy was begun ten days later and completed in two weeks. Eight weeks later the ascites was again evacuated and a second series of irradiation given. There was no re-accumulation of fluid following this series. Two more series of roentgen therapy were given at sixty-day intervals. In January, 1932, thirty-

three months after the first operation, Dr. Keene repaired a ventral hernia and at the same time he was able to remove the huge primary malignant growth, involving both ovaries. Another series of irradiation was begun ten days later. At the present time, five years after the first operation, the patient is in excellent health with no evidence of disease in the abdomen or pelvis.

#### TECHNIC OF TREATMENT

The patients were given irradiation over the primary site, the lymphatics draining it, and the possible peritoneal transplants. Our plan of treatment consisted of administering to the patients in Group III the maximum therapy, depending upon the skin tolerance and the general condition of the patients. This was continued as long as palpable evidence of the disease remained. The intervals between the treatments were extended as long as permissible, in order to preserve the effects of irradiation. This seems to be an important point as it is well recognized that malignant tissue does become radioresistant. One patient received approximately 7,000 r. into the center of the pelvis during a period of five years. Patients in Group II were given two series of treatments at intervals of six weeks, through two, three, or four portals about the pelvis, abdomen, and back, depending upon the size of the patient, and through an additional upper lumbar and lower thoracic portal. Further treatment depended entirely upon the course of the disease. Those in Group I received one series of treatments through the 20 by 20 cm. portals as outlined. A series consisted of 1,600 r. as measured in air delivered to each portal about the pelvis and abdomen and 800 r. to the upper lumbar one. The factors were: 200 KVP. and 4 ma. (since 1932, 165 KVP constant potential and 15 ma.); the filtration was 0.5 mm. Copper plus 2 mm. Al.; and the target skin distance was 50 cm. The treatments were given in divided doses using the saturation method. The rapidity of delivering the dosage depended to a large extent upon the general condition of the patient and the amount of irradiation sickness if such were present.

#### CONCLUSIONS

This study shows that in the treatment of ovarian carcinoma, roentgen therapy has a two-fold value: first, the prolongation of life; second, the relief of symptoms as evidenced by its beneficial effect upon pain, ascites, and tumor formation.

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#### DISCUSSION

DR. EUGENE P. PENDERGRASS.—All of the cases reported received post-operative irradiation, except one. In that patient, Mrs. E. B., I feel justified in regarding her irradiation as preoperative. If the result can be regarded as indicative of what may happen in patients with inoperable carcinoma of the ovaries receiving preoperative irradiation, it may be necessary in the future to change some of our present concepts as to the best time to operate upon the patient.

We are convinced that removal of the primary malignancy will enhance the value of irradiation. On the other hand, it may be better to give a preoperative course of irradiation after the diagnosis has been established.

The procedure that may come to be the one of choice and suggests itself to me is: (a) operative and pathologic diagnosis; (b) irradiation over the primary malignancy.

nancy and lymphatic channels draining it; (c) operative removal of the primary malignancy six to twelve weeks later or at such time as the patient's condition may indicate; (d) postoperative irradiation as indicated. I realize that there is only one case upon which to base such an opinion, but the result in this case has been so satisfactory that it deserves further trial. Furthermore, preoperative irradiation may render a lesion, otherwise inoperable, at least palliatively operable.

DR. LEWIS C. SCHEFFEY.—The work described is very much in line with the results reported from the Jefferson Hospital several months ago. From that study I can heartily endorse the conception of following operative treatment with irradiation, and agree that exploratory section should be the primary step, at least.

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## A PHARMACOLOGIC STUDY OF THE UTERINE FISTULA OF THE UNANESTHETIZED RABBIT\*

### I. PITUITRIN

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REYNOLDS (1930) has demonstrated the difference in the uterine responses of the unanesthetized animal to large doses of pituitrin and pitocin. Our study was undertaken to determine more completely the response of the uterine fistula to extracts of the posterior lobe of the pituitary gland and to identify the factor responsible for the difference in uterine response to pituitrin and to pitocin.

### EXPERIMENTAL PROCEDURE

Female rabbits weighing 2.5 to 3.5 kilograms were used in these experiments. Immediately postpartum the young were removed.†

All extract dilutions were made with a tuberculin syringe in normal saline. All injections were made in the marginal ear vein. The pituitary extracts used in this study were pituitrin, pitocin, and pitressin, which were generously supplied by Parke, Davis and Company.

*Record 1.*—Ten minutes elapse between end of Record A and beginning of Record B, a period of uterine inactivity.

1. 0.1 c.c. pituitrin.
2. 0.1 c.c. pituitrin ten minutes after initial pituitrin injection.
3. 0.1 c.c. pituitrin twenty-one minutes after previous pituitrin injection.

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\*This study was aided by a grant from the Committee for Research in Problems of Sex of the National Research Council. The funds were granted to Dr. H. C. Bazett and administered by Dr. M. H. Friedman.

Read at a meeting of the Obstetrical Society of Philadelphia, May 3, 1934.

†The association of regular uterine motility and estrus at this time has been demonstrated by Reynolds and Friedman (1930). The rabbit uterus is bicornuate. Each uterine horn forms a cylindrical hollow tube. The fundal portion of each uterine horn enters the upper end of the vagina. Under ether anesthesia a midline incision was made and the vagina so transected that a small cuff of vaginal mucosa surrounded the orifices of the uterine horns. The orifices of the uterine horns were brought out and sutured to the anterior abdominal wall. Four days after operation a small balloon was inserted into the fistula and by means of a Brody bellows uterine contractions of the unanesthetized intact uterine fistula were recorded on a kymograph (Reynolds and Friedman, 1930).

*Record 2.*—Records C and D are continuous.

1. 0.1 c.c. pitocin.
2. 0.1 c.c. pitocin eleven minutes after previous injection of pitocin.

*Record 3.*—Records E and F are continuous. Five minutes elapse between end of Record F and beginning of Record G.

1. 0.1 c.c. pitocin.
2. 0.1 c.c. pitressin.
3. 0.1 c.c. pitocin twelve minutes after previous pitressin injection.
4. 0.1 c.c. pitocin twenty-eight minutes after previous pitressin injection.

*Record 4.*—Twenty-two minutes elapse between end of Record A and beginning of Record B. Records B and C are continuous.

1. 0.2 c.c. 1:50 pituitrin.
2. 0.2 c.c. 1:50 pituitrin ten minutes after initial pituitrin injection.
3. 0.2 c.c. 1:50 pitocin.
4. 0.2 c.c. 1:50 pitocin nine minutes after initial pitocin injection.
5. 0.2 c.c. 1:50 pitressin eight minutes after previous pitocin injection.
6. 0.2 c.c. 1:50 pitocin eight minutes after previous pitressin injection.

## RESULTS

*A. Injection of a Single Large Dose of Pituitrin.*—The injection of a large dose, 0.1 c.c., of pituitrin (10 international units per c.c.) containing both the oxytocic and pressor factors, produces an immediate uterine tetanus lasting from three to five minutes. This is followed by a decrease in tonus level and complete uterine inactivity persisting from twenty-five to thirty minutes, after which interval the original uterine activity reappears (Fig. 1).

*B. Injection of a Single Large Dose of Pitocin.*—The injection of a large dose, 0.1 c.c., of pitocin produces an immediate uterine tetanus lasting from three to five minutes, and this is followed immediately by large regular uterine contractions with no period of uterine quiescence such as is present after the tetanus following the injection of 0.1 c.c. of pituitrin (Fig. 1).

*C. Injection of a Large Dose of Pitocin Followed by a Large Dose of Pitressin.*—If immediately following the cessation of uterine tetanus resulting from the injection of 0.1 c.c. of pitocin, 0.1 c.c. of pitressin (10 units per c.c.) be injected, there is a rapid loss of uterine motility and the tonus level of the uterus is decreased. Normal uterine activity reappears from twenty-five to thirty minutes after the injection of pitressin. This response to the injection of pitocin followed by pitressin is identical with that obtained on the injection of a single large dose of pituitrin (Fig. 1).

*D. Repeated Large Doses of Pituitrin.*—The injection of a second dose of pituitrin, 0.1 c.c., after the return of normal uterine activity (twenty to thirty minutes) produces a uterine response identical with that originally obtained. However, if the second dose of pituitrin be injected ten minutes after the initial dose, during the period of uterine inactivity, no uterine response is obtained (Fig. 1).

*E. Repeated Large Doses of Pitocin.*—If a similar dose of pitocin, 0.1 c.c., be injected ten minutes after the initial dose of pitocin, a uterine response, identical with that originally obtained, is elicited (Fig. 1).

*F. Large Dose of Pitocin Injected During the Period of Uterine Quiescence Following Injection of Pitressin.*—If a large dose of pitocin, 0.1 c.c., be injected ten minutes after the injection of 0.1 c.c. of pitressin (during the period of complete uterine inactivity), no uterine response is obtained. This failure to obtain a uterine response with pitocin, during the interval of uterine inactivity produced

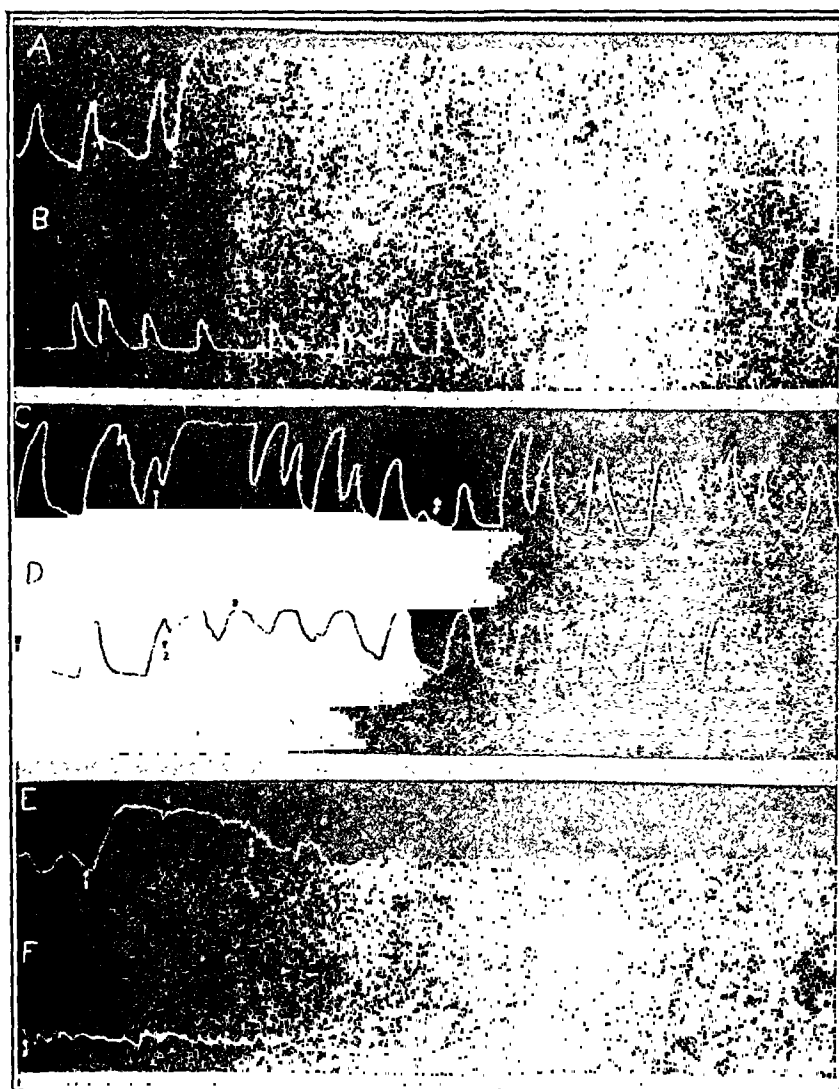


Fig. 1.

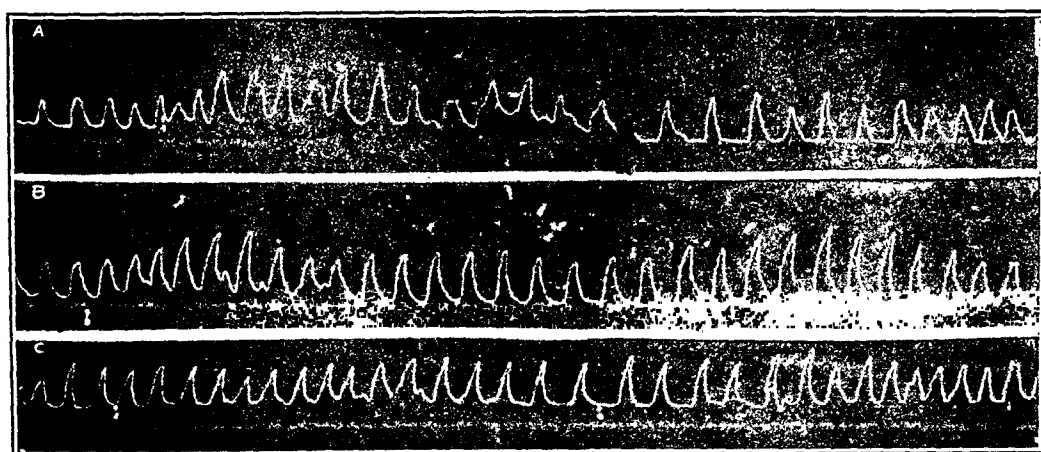


Fig. 2.



by a previous injection of pitressin, is similar to the inability of the uterus to respond to a second dose of pituitrin during the period of uterine quiescence succeeding a previous pituitrin injection (Fig. 1).

*G. Injection of a Small Dose of Pituitrin.*—The injection of a small dose of pituitrin (0.2 c.c. of 1:50 dilution) produces an increase in uterine tonus and an increase in the rate of uterine contractions which change persists from two to four minutes, and then in contrast to the uterine inactivity which is produced by a large dose of pituitrin, the uterine motility quickly returns to its normal character (Fig. 2), i.e., there is no subsequent period of decreased activity.

Nevertheless, the injection of an equal dose of pituitrin ten minutes later, even though uterine motility is normal, produces *no* uterine response; but if twenty minutes elapse between injections, repeated responses, each slightly less than the previous one, may be obtained.

*H. Injection of a Small Dose of Pitocin.*—The injection of a small dose of pitocin (0.2 c.c. of 1:50 dilution) produces an increase in uterine tonus and an increase in the rate of uterine contractions which persists for two to four minutes and is followed by a return to normal uterine motility. This response is identical with that obtained on the injection of a similar dose of pituitrin.

However, in contradistinction to the results obtained with repeated small doses of pituitrin, successive identical uterine responses may be obtained in response to small doses of pitocin (0.2 c.c. of 1:50 dilution) injected at ten-minute intervals (Fig. 2).

*I. Injection of a Small Dose of Pitressin.*—The injection of a small dose of pitressin (0.2 c.c. of 1:50 dilution), immediately after the response obtained with a small dose of pitocin (0.2 c.c. of 1:50 dilution), produces no change in uterine motility. In spite of the fact that no change in uterine motility is produced by this injection of pitressin, the injection of pitocin (0.2 c.c. of 1:50 dilution) ten minutes afterward produces *no* uterine response (Fig. 2). If pitocin is again injected ten minutes later (twenty minutes after the previous pitressin injection) a definite uterine response is obtained.

*J. Tolerance Induced by Repeated Injections of Pituitrin.*—By starting with a small dose (0.2 c.c. of 1:50 dilution) of pituitrin and then injecting successively larger doses at ten-minute intervals, it is found that only the initial injection evokes a uterine response, and following this initial response no further change is produced in uterine motility. This may be continued until the injection of 0.1 c.c. of pituitrin, which normally elicits a maximal uterine response, has no effect either on uterine tonus or motility. This state of induced tolerance to both the oxytocic and uterine inhibiting factors present in pituitrin persists for an interval of sixty minutes following the last injection, after which period the injection of 0.1 c.c. of pituitrin will produce a maximal uterine response.

#### DISCUSSION

The results of Reynolds (1930), who first demonstrated the difference in response of the uterine fistula to large doses of pituitrin and pitocin, have been confirmed in this study. Blair-Bell, Datnow and Jeffcoate (1933), using the rabbit uterine fistula preparation employed in these experiments, have also reported that pituitrin, after producing an immediate increase in uterine tonus, induced a temporary inhibition of uterine motility which persisted for an interval of ten to fifteen minutes.

That pitressin is the factor acting to abolish uterine activity after the initial tetanus obtained on the injection of a large dose of pituitrin, is apparent from an examination of Fig. 1. Pituitrin, containing both the oxytocic and pressor factors, causes an initial uterine tetanus followed by a period of uterine inactivity. Pitocin, however, containing only the oxytocic factor, after producing an initial tetanus, does not act to inhibit uterine motility. Pitressin, injected immediately after pitocin, abolishes all uterine activity for an interval similar to that present after the injection of pituitrin. Pitressin must, therefore, be the factor present in pituitrin which so modifies the uterine response to the oxytocic factor present, that uterine quiescence succeeds the initial uterine tetanus.

It may be of further interest to note that in several experiments the injection of pitressin in large doses immediately relaxed the uterine tetanus produced by the intravenous injections of adrenalin, ergotamine, and cocaine. It may, therefore, be said that pitressin will induce uterine relaxation regardless of whether the uterus is exhibiting spontaneous activity or tetanus induced by injection of adrenalin, pitocin, ergotamine, or cocaine.

Previous workers, Frankl-Hochwart, and Fröhlich (1910), and Fühner (1913) have demonstrated a state of uterine tolerance to repeated injections of posterior lobe extract. Bourne and Burn (1927) have noted, on repeating injections of pituitrin in the parturient woman, that no response was obtained to the second injection of pituitrin if the interval between injections was less than one hour. Blair-Bell, Datnow and Jeffcoate (1933) using the rabbit uterine fistula also demonstrated the production of a state of uterine tolerance to repeated injections of pituitrin, the second injection of pituitrin having no effect unless a certain interval of time had elapsed between the first and subsequent injections.

That pitressin is the factor in pituitrin which induces a state of uterine tolerance to subsequent injections of pituitrin is evident from an examination of Fig. 2. After the initial increase in uterine motility produced by a small dose of pituitrin, uterine motility returns to normal. A subsequent injection of pituitrin elicits no response until a certain interval of time elapses between the injections. In contrast to this tolerance, repeated injections of pitocin each produces an increase in uterine tonus identical with that produced by a single, similar small dose of pituitrin. However, the injection of a small dose of pitressin, even though uterine motility is not altered, abolishes all response to subsequent injections of small doses of pitocin for an interval equal to the refractory period following a small dose of pituitrin. It must, therefore, be concluded that the pressor factor (pitressin) in pituitrin is the substance responsible for the failure to obtain repeated uterine responses to a series of injections of pituitrin.

With the injection of large doses of pituitrin, uterine tolerance to a repeated dose of pituitrin apparently was associated, as far as time relationships were concerned, with the period of uterine inactivity follow-

ing the initial tetanus. However, when small doses of pituitrin were injected so that the pressor fraction of the dose of pituitrin injected had no influence on uterine motility, it was quite apparent that the uterine tolerance to repeated doses of pituitrin was developed regardless of the state of uterine motility, be it depressed or normal in character.

The production of a state of induced uterine tolerance to both the oxytocic and pressor factors in pituitrin has been demonstrated by injecting successively larger doses of pituitrin at ten-minute intervals. Under this treatment the uterus becomes refractory to both the uterine stimulating (oxytocic) factor and the uterine inhibiting (pressor) factor, so that 0.1 c.c. of pituitrin, which normally elicits a maximal uterine response, has no influence on uterine motility.

The data obtained in these experiments are not in accord with the results reported by Robson (1933) using excised muscle strips of both rabbit and human uteri. In these experiments *in vitro*, uterine responses were elicited by both pitressin and pitocin. However, the inadequacy of recording and evaluating uterine responses obtained by this method has been discussed by Reynolds (1931) and Van Dyke and Hastings (1927). Blair-Bell, Datnow and Jeffcoate (1933) using the uterine fistula preparation in lightly anesthetized rabbits state that, "Pitressin is quite as effective as a uterine stimulant as is pitocin." In the dose used in their experiments, 0.2 c.c. intravenously, we have repeatedly demonstrated that there is sufficient oxytocic substance present as a contaminant to produce an initial uterine tetanus which is similar to the first portion of the response to pitocin, but in every instance this initial tetanus is followed by a period of uterine inactivity. Adair and Davis (1934) using postpartum women, found no difference in the uterine responses evoked by pituitrin, pitocin, and pitressin. It is quite possible that the dose of pitressin injected contained sufficient oxytocic substance to produce a uterine response in the extremely sensitive parturient uterus. The failure to obtain uterine relaxation after the initial tetanus may be due to a species difference in uterine susceptibility to the uterine relaxing action of pitressin, or to the fact that the dose required for relaxation of the uterus is relatively much greater in the human being than in the rabbit.

Bourne and Burn (1928), however, found that whereas pitocin had a powerful stimulant action, pitressin even in large doses (12.5 International units) had no effect on the uterus in labor. The method of recording used in their work was essentially the same as that used by Adair and Davis.

Although the results of Adair and Davis (1934) with pitressin on the motility of the human uterus are not in accord with the results obtained with pitressin in the rabbit, there is nothing in the results obtained by these workers to indicate that the pressor factor is not responsible for the development of uterine tolerance. There can be little doubt that tolerance to repeated injections of pituitrin does occur in the human uterus, as has been graphically demonstrated by Bourne and Burn (1927). Inasmuch as the development of tolerance in the rabbit is not necessarily associated with any change in uterine motility in either direction, it is entirely possible, if not probable, that the development of a state of

tolerance even in the human uterus is due to the pressor fraction, although the influence of the latter on motility is not identical in the human and the rabbit uterus.

Therefore, since this development of uterine tolerance in the rabbit has been shown to be a property of the pressor fraction of pituitrin, and to be entirely independent of any action it may have on uterine motility, it is suggested that pitocin rather than pituitrin be the drug of choice in the medical induction of labor and in the management of the third stage of labor; at least until more satisfactory data are available on the action of these drugs on the human uterus.

#### CONCLUSION

In the rabbit uterus:

1. Large doses of pituitrin produce an uterine tetanus followed by a period of uterine inactivity persisting for twenty to thirty minutes.
2. Large doses of pitocin produce a uterine tetanus followed by normal uterine motility.
3. The uterine quiescence following the initial tetanus produced by pituitrin is induced by the pitressin fraction.
4. Pitressin divorced from its motility inhibiting character by the injection of a minimal dose has been demonstrated to be responsible for the absence of a response to a second injection of pituitrin, unless a definite interval of time elapses between injections.
5. The induction of uterine tolerance is independent of any action of these drugs on uterine motility.

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THIRTY-SIXTH AND SPRUCE STREET

#### DISCUSSION

DR. MAURICE H. FRIEDMAN.—There does not seem much to say except that the joke seems to be on us a bit. During the work, we saw this astonishing ability of pitressin to relax the uterus. We could take a uterus, in spasm from any of the drugs that would contract the uterus; we could then by the simple procedure of injecting pitressin, completely relax it. We thought that, perhaps, if it worked like that in the human being, obstetricians and gynecologists would have a valuable aid for use in relaxing the uterus and in the treatment of dysmenorrhea. But this again shows the wisdom of being a bit cautious of transferring results obtained in rabbits to human beings. The conclusion that should be drawn, but from which we refrained, was that the rabbit is, after all, not human.

# A COMPARATIVE STUDY OF LIPIODOL INJECTION AND AIR INSUFFLATION IN STERILITY

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UTEROSALPINGOGRAPHY has now merited a place in the diagnostic armamentarium of the gynecologist.

W. H. Cary first proposed and described a method of testing the patency of the fallopian tubes in 1913 by the transuterine installation of collargol, and the subsequent roentgen ray demonstration of its presence in the peritoneal cavity. Kennedy in 1923 used a 20 per cent solution of sodium iodide. Rubin first used collargol solution and later other opaque media to demonstrate the patency or occlusion of the fallopian tubes. In the past few years lipiodol (40 per cent iodine in a vegetable oil) has displaced these substances in the roentgenologic demonstration of the uterus and tubes. C. Heuser of Buenos Aires described radiography of the uterine cavity with lipiodol and claimed priority for this method, stating that his first report appeared in 1921 and that Wintz and Beclere of France did not mention their work until 1925. S. A. Robins says that uterosalpingography is now applicable not only in sterility but in routine examinations and speaks of it as a simple and harmless office procedure. Darbois and Beclere have widened their indications for the use of uterosalpingography, and utilize it in all their sterility cases to study the patency of the fallopian tubes and to localize any obstruction present. J. Iribane and N. Cappizzane use lipiodol injections of the uterus and tubes in all cases of sterility.

The following technic was employed in a series of 32 cases of sterility as a check on previous air insufflations in the same patients:

The test is performed about ten days before or after the menstrual period. With the patient in the dorsal position and the bladder empty, a bivalve speculum is introduced into the vagina which is wiped dry of secretion. The cervix is painted with tincture of iodine or 2 per cent mercurochrome and is then grasped with a tenaculum. The position, size, shape, and mobility of the uterus is determined previously by a bimanual examination. Patients with any acute pelvic inflammation or marked tenderness of the pelvic organs are deemed unadapted to this procedure. A Keyes-Ultzmann cannula with a rubber acorn on the shaft is introduced into the cervical canal so that the acorn occludes the cervix and prevents leakage. From 8 to 10 c.c. of warmed lipiodol is drawn into a Luer syringe, attached to the cannula, and without undue pressure slowly injected into the uterus. After waiting from three to five minutes with the cannula in situ an x-ray plate is taken, holding the cannula in position during the exposure. A second plate is taken after a five-minute interval. The cannula is removed and the oil wiped out of the vagina. The patient is instructed to return within twenty-four hours for another x-ray plate, to determine the presence of oil in the peritoneal cavity. It has been our experience that the patients with patent tubes have no discomfort and the oil meets with very little resistance during injection.

The technic of the transuterine insufflation test used in our clinic is that described and modified by Dr. Adolph Jacoby. With the patient in the dorsal posi-

tion a bivalve speculum is introduced into the vagina and the cervix exposed. All excess of secretion is wiped away. The cervix is painted with iodine or mercurchrome. No tenaculum is placed on the cervix unless it is necessary to steady and fix the cervix. The Jacoby instrument with a manometer screwed to the side outlet and a 40 c.c. Luer syringe locked at the other end is introduced into the uterine cavity. Care is taken not to traumatize the mucosa. After introduction the obturator is held tightly against the external os by steady and firm pressure. The piston of the syringe is slowly and steadily squeezed, forcing air through the cannula while the operator watches the pressure indicated on the manometer.

If the tubes are patent, the manometer reading will drop after reaching 100 mm. or more and the air will continue to flow into the peritoneal cavity through the tubes at reduced pressure. In nonpatent cases the pressure will rise to 200 mm. without a subsequent drop. In the patent cases the patient will complain of shoulder pain on arising or soon thereafter.

Thirty-two patients with primary and secondary sterility were examined by both air insufflation and lipiodol injection. In twenty-five of the thirty-two patients examined the findings by air insufflation were confirmed by x-ray after lipiodol injection. In one of these 25 patients, three air insufflation tests were performed; the first test gave a high pressure reading of occlusion; the second test, one of partial obstruction with subjective pain; and the third test showed the tubes to be patent. This patient may have been one of the group in which the therapeutic value of air insufflation becomes evident. Three patients gave readings of occlusion with air insufflation, whereas the salpingogram showed patency. In these, one had three air insufflation tests; one had two air insufflation tests; and one had one air insufflation test. The lipiodol injection was made after the last air insufflation test and one might assume that the tubes may have been opened by the air pressure. Three patients gave readings of partial occlusion with the air test, although salpingograms showed that the tubes were patent. Here the information obtained from the air test was of greater value than that derived from the lipiodol injection. In one patient the air test indicated partial occlusion and salpingogram findings showed the tubes to be closed. In this instance one might suspect that the air could pass through the partially occluded tubes, whereas the greater density of the oil obstructed its passage into the peritoneal cavity. The discrepancy in these seven cases raises the question of the accuracy of the x-ray interpretation. Sometimes the reading of a salpingogram requires a certain amount of presumption on the part of the diagnostician.

Four of the thirty-two patients who had transuterine lipiodol injections performed suffered from subsequent sequelae.

CASE 1.—Aged thirty-eight, married five years. Primary sterility. Air insufflation test indicated that the fallopian tubes were patent. On Dec. 16, 1931, a transuterine lipiodol injection was performed and showed patency of the tubes. Several days following the salpingogram patient complained of severe backache. March 31, 1932, patient complained of pain in the left flank and dysmenorrhea which she dated from the time of the lipiodol injection. Vaginal examination showed the fundus and body of the uterus pulled upward and to the left, uterus tender and marked tenderness in the posterior parametrium. April 2, 1932, three and one-half months after salpingogram radiographic report showed a small quantity of contrast medium still present in the pelvis.

CASE 2.—Aged thirty-one, married ten years. Primary sterility. Air insufflation test showed the tubes to be patent. Nov. 18, 1931, salpingogram confirmed the air test by report of contrast medium on both sides of the pelvis. Patient com-

plained of pain in the pelvis following lipiodol injection. Dec. 10, 1931, twenty-two days after lipiodol injection radiographic report showed contrast medium to be present in the culdesac.

CASE 3.—Aged thirty-eight, married five years. Primary sterility. Air test showed the tubes to be patent. Nov. 13, 1931, a salpingogram was made. Radiographic report stated that neither tube is definitely visualized but a large globule of contrast medium was seen in the pelvis on the left side. Dec. 3, 1931, patient developed a marked leucorrhea. Pelvic examination revealed a palpable tube and ovary on the right side. Left tube and ovary enlarged to the size of a small apple. April 16, 1932. Five months later a flat plate was taken and the radiographic report showed a quantity of contrast medium on the left side of the pelvis.

CASE 4.—Aged thirty-one, married ten years. Primary sterility. Air test showed the tubes were patent. Nov. 18, 1931, transuterine injection of lipiodol. Radiographic report read "contrast medium seen in peritoneal cavity on both sides," suggesting patency of both tubes. Dec. 10, 1931, radiographic report showed contrast medium in the culdesac approximately three weeks after the injection. This patient came to operation Nov. 17, 1932, about one year after lipiodol injection. Operative findings at the time were as follows: On opening the abdomen a fair quantity of free serous fluid was present. The peritoneal surface appeared to be somewhat irritated. Tubes were found to be normal and patent. The right ovary which was enlarged was resected. The fluid in the abdominal cavity was suctioned off. Surgeon's note: Peritoneal irritation and free fluid in peritoneal cavity is probably accounted for by the previous injection of iodized oil.

TABLE I. THIRTY-TWO CASES OF STERILITY TESTED BY AIR INSUFFLATION AND LIPIODOL\*

	CASES	AVER. YR. MAR- RIED	YOUNG- EST	OLD- EST	AIR TEST			SALPINGOGRAM AIR TEST AND SALPINGOGRAM				
					P.	N.P.	P.O.	P.	N.P.	P.O.	POSITIVE	NEGATIVE
Primary sterility	18	7.11	21 yr.	38 yr.	4	9	1	4	9	1	25	7
Secondary sterility	14	9.44	24 yr.	41 yr.	5	6	0	5	6	0		

SEVEN CASES OF STERILITY TESTED BY AIR INSUFFLATION AND LIPIODOL WITH VARIED FINDINGS

NO. OF CASES	TYPE OF STERILITY	AIR TEST			SALPINGOGRAM		
		P.	N.P.	P.O.	P.	N.P.	P.O.
7	Primary	0	3	4	6	1	0

\*P, Patent; N.P., nonpatent; P.O., partial obstruction.

Note: Sixteen of these cases had two or more air tests.

R. J. Heffman in a review of the literature notes that complications consist chiefly of infections but there have also been a number of deaths following the use of salpingography.

W. Odenthal in one of his cases injected 4 c.c. of iodopin (iodized oil), without an immediate reaction, the patient leaving the hospital three days after the injection of the oil, but within ten days she developed symptoms of peritoneal irritation with fever which subsided after three weeks of treatment.

Barton C. Hirst mentions one accident occurring in a woman who urgently requested operation twenty-four hours after a lipiodol test. Distal salpingostomy and suspension of the uterus were performed satisfactorily but a streptococcus peritonitis caused death. It is interesting to note that this operation was preceded by one in which a streptococcus of the same strain was found.

Gauss in a review of the literature states that in about 3,000 cases in which iodized oil was injected there were five deaths and thirteen additional cases of infection.

E. Gajzage reported a case in which death resulted from oil embolism after uterosalpingography, proved at autopsy. The oil was accidentally injected into a vein which was injured at the time the cannula was inserted into the uterus.

I. C. Rubin, whose researches and contributions to the study of sterility are extensive, reported 132 cases in whom lipiodol injections were performed. Six patients developed peritoneal inflammation of a mild grade, and three developed pelvic abscesses requiring surgical intervention. Such results in the hands of a gynecologist of Rubin's experience in this particular field would doubtless prove more serious in the hands of the less experienced.

Joseph L. Baer reports a case in which he had opened the abdomen of an apparently normal patient, free from elevation of temperature, with the intention of doing a Gilliam suspension of the uterus, but in whom he found both tubes dripping free pus from the fimbria. Among other thoughts, he suggests what might have happened had he attempted a patency test in that patient. One can also imagine what might have happened if a lipiodol injection had been made.

The writer had his attention called to a patient, injected with lipiodol by a competent gynecologist, who left his office and upon arriving home was seized with severe abdominal pain. She was removed to a hospital and died a few days thereafter of a fulminating peritonitis.

Emil Ries at a meeting of the Chicago Gynecological Society presented a specimen showing the effect of lipiodol injection on the tubes. This patient was tested for sterility by air insufflation on three different occasions and in each instance the air failed to pass through. This was followed by a lipiodol injection and the x-ray plate seemed to show that the oil had passed into the peritoneal cavity. There was no reaction until two months after the lipiodol injection, when the patient began to feel sick and have pain. She was operated upon and the findings showed extensive adhesions, so that none of the pelvic organs were visible when the abdomen was opened. Both tubes were dissected out and showed an interesting microscopic picture. Large areas of the tubal mucosa had disappeared while elsewhere the lining epithelium was normal. An enormous number of giant cells were present, in the midst of which were found structureless greenish masses of a homogeneous and granular character. Some of the cells contained small particles of this greenish substance. These conditions were found in both tubes; in the open as well as in the closed.

A. F. Lash secured a specimen of bicornate uterus with retention of lipiodol in the pelvis twenty-two months after injection. At laparotomy the omentum was found partly adherent to the right horn of the uterus, to the junction of the two horns, to the bladder and to three masses in the culdesac. After freeing the omentum the three masses which contained lipiodol were removed. Examination of these masses showed no iodine on direct tests, but iodine was demonstrated after breaking down the lipiodol. Lash contends that there was a bilateral salpingitis, with a foreign body reaction produced by the lipiodol, which had been present in the pelvis for twenty-two months.



R. J. Hoffman emphasizes the fact that iodized oil preparations may give rise not only to infections but also to fatalities, and that the retention of particles of iodized oil within the tubes may cause local damage.

Barton C. Hirst believes that a lapse of time is essential before operating on a patient who has had a lipiodol injection.

J. Novak insists that salpingography should be reserved for a few special cases. He describes a case in which salpingography showed both tubes to be closed. At operation the tubes were opened and the oil removed, but infection set in and the patient died. At autopsy it was evident that the iodized oil had produced not only inflammatory changes of the tubes but also a foreign body reaction in the peritoneal cavity, and peritonitis. He also mentions another case in which iodized oil was found two years after salpingography. He believes that salpingography should never be used routinely in cases of sterility, and that its use should be limited to rare cases.

Brooke M. Anspach does a lipiodol injection in sterility cases after an air insufflation test has demonstrated a closure, and some operative procedure for its correction is desired by the patient.

Hazelhorst concludes that while uterosalpingography is a valuable method it is not without danger, and he does not consider the presence of free iodized oil in the peritoneal cavity as harmless.

Curtis is of the opinion that the instillation of iodized oil is a valuable procedure but should be used with great caution. He has seen cases in which the peritoneal reactions were very severe.

In view of my personal results in a limited number of cases I believe that despite the simplicity and facility of uterosalpingography, trans-uterine air insufflation should be the method of choice for the determination of tubal patency in cases of sterility, and that uterosalpingography should be reserved for unusual special cases. With simple insufflation it is easy to determine not only whether the tubes are occluded or patent but also whether one or both tubes are open (stethoscope). In addition, the site of obstruction may be revealed by the localization of pain, and tubal spasm by the use of the kymograph.

Great selectivity and care should be exercised in sterility cases before the injection of lipiodol, and uterosalpingography should be the last step rather than the first in the search for the causative factor of sterility. That the injection of lipiodol is not entirely innocuous and may result in morbidity is substantiated by my own experience and that of others. In the diagnosis and localization of obstruction of the fallopian tubes in cases of sterility, the sequelae may prove harmful to the patient, if the method is applied indiscriminately.

#### CONCLUSIONS

1. A review of the literature indicates that routine lipiodol injections are not harmless and that as a diagnostic method it carries a morbidity and mortality, even though small.

2. The use of lipiodol injection in cases of sterility is unwise until a complete history, careful bimanual examination, endocrine survey, air

insufflation tests, study of the vaginal chemistry, investigation of cervical pathology, and the fertility of the male partner have been investigated.

3. Operations on tubes should be postponed for several months after lipiodol injections.

4. In sterility cases in which one tube is occluded or both tubes show partial occlusion as demonstrated by air insufflation, lipiodol injections should be used cautiously, as complete occlusion may result and thus defeat the primary objective.

5. Air insufflation yields the desired information regarding the condition of the tubes, without harm and subsequent sequelae. This has been our experience in a large number of cases.

6. The contention that lipiodol may remain in the peritoneal cavity for one year or more and result in serious pathology has been verified by personal experience and the publications of others.

7. Misinterpretation is not unlikely in the reading of salpingograms by the inexperienced; errors are few after transuterine insufflation.

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de Torres, E. M.: Oil Embolism in Hysterosalpingography, Revue franç. de Gynécologie et Obst. 29: 218, 1934.

Pelvic infection may occur after the use of hysterosalpingography but the most frequent accident is penetration of lipiodol into the blood vessels. In most cases, this accident remains unnoticed because it produces no visible symptoms. An excessive pressure is not necessary to bring about this accident. Among the causes are hypoplasia of the uterus with tubal occlusion and recent hemorrhage. de Torres believes that recent hemorrhage is the most frequent cause. The small open veins permit the ready access of lipiodol which is quickly carried away by the blood stream from the portal of entry. The author, therefore, warns against the use of hysterosalpingography in cases of uterine bleeding. He points out that we have other means of exploring the uterine cavity which are safer, for example curettage. The fact that oil embolism is usually harmless should not be a reason to disregard its possible dangers.

J. P. GREENHILL.

# IS THE LOWER UTERINE SEGMENT EXCLUSIVELY A CLINICAL PHENOMENON?

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SINCE the writer in 1928 published a paper<sup>1</sup> on the origin of the lower uterine segment wherein anatomic and histologic evidence was presented to support the contention that the lower uterine segment is made up of both the uterus (or that portion of the nonpregnant uterus designated by Aschoff<sup>2</sup> as the isthmus) and the dilated cervical canal, other articles on the subject appeared, the most notable of which is that of Frankl<sup>3</sup> where among other important data, he makes the same affirmation.

The contention sustained by Frankl<sup>3</sup> and others that the firm attachment of the uterine peritoneum does not correspond mathematically to the upper limit of the isthmus, as originally asserted by Braune,<sup>4</sup> may be true when the differences in the uterine mucosa are made the sole criterion of division between the uterine segments entirely disregarding the muscular disposition or behavior. Nevertheless, I am of the opinion that such an external landmark is—for practical purposes, as for instance in operations on the uterus, the determination of the site of placental implantation or of uterine rupture—of sufficient accuracy to indicate the limit of either the isthmus of the nonpregnant or the lower uterine segment of the puerperal uterus. The lower limit of the isthmus (or lower uterine segment) is also recognizable with the naked eye by the upper border of the arbor vitae or plica palmatae of the cervical mucosa.

## FORMATION OF THE LOWER UTERINE SEGMENT

There has been some confusion in obstetric teaching as regards the formation of the lower uterine segment. When Braune<sup>4</sup> and later, Bandl<sup>5</sup> described what is now known as Bandl's ring and emphasized its clinical importance, denoting the division of the uterus into two segments, namely, superior and inferior, textbooks began to assert that the lower uterine segment is a clinical phenomenon not manifested until labor and only during active contraction of the uterus. At the same time, it was taught, and rightly, that in cases of placenta previa the placenta or part of it is attached to the lower uterine segment which phenomenon a priori presupposes the actual existence of the lower uterine segment at the beginning of pregnancy when placental development takes place. If its existence is denied until labor contractions set in, how could the

placenta be implanted in it? Stieve<sup>6</sup> has clarified this confusion when he showed that during pregnancy, the isthmus uteri, which in pregnancy constitutes the uterine portion of the fully formed lower uterine segment, is gradually drawn up to the ovum chamber. By this he means that the line of constriction separating the corpus from the isthmus uteri is gradually effaced. The examination of specimens at different stages of pregnancy and even during menstruation show that effacement of constriction at the upper end of the isthmus begins to be initiated as early as the pregravid stage when the predecidual formation takes place. Frankl<sup>3</sup> states that from the second month of pregnancy, the limit of the isthmus begins to disappear and becomes unrecognizable in the third month when it fully passes into the upper compartment of the uterus.

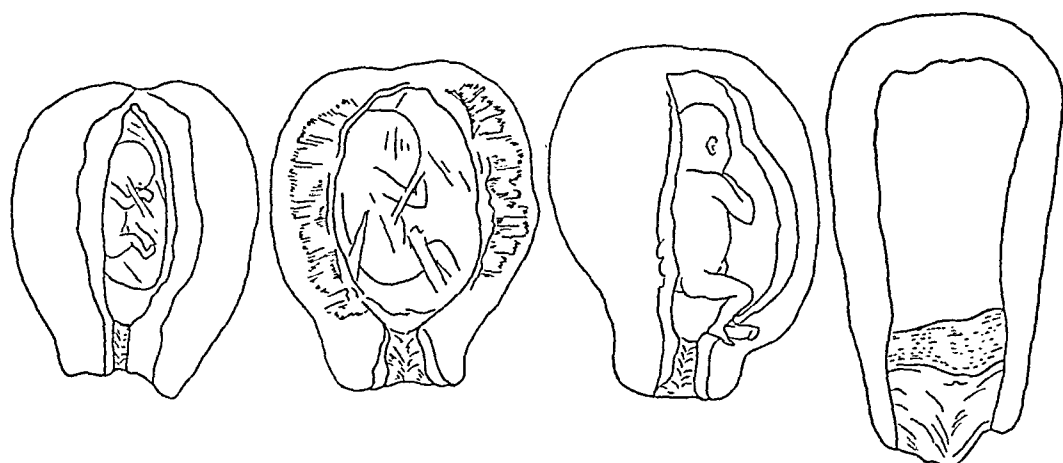


Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 1.—Two and one-half months' pregnancy. The upper isthmus constriction is erased.

Fig. 2.—Three months' pregnancy. There is no constriction between the upper and lower uterine segments.

Fig. 3.—Three and one-half months' pregnancy. There is no constriction between the upper and lower segment of the uterus.

Fig. 4.—Postpartum uterus showing the relative length of the lower uterine segment and the cervix.

Figs. 1, 2, and 3 show that the isthmus has become part of the ovum chamber and that the only constriction recognizable is the histologic internal os or the upper limit of the cervix.

The above facts conclusively establish that the lower uterine segment, perhaps due to hormonal influences, begins to be formed as early as the implantation of the ovum, and, because it does so, one can understand how it is that sometimes part or most of the placenta may be implanted in it. It is admitted, however, that the complete formation and manifestation of its functional rôle does not take place until the entire cervical canal is completely dilated when the cervix in conjunction with that which was the isthmus takes on a passive or dilative action as a result of effective contraction of the upper uterine segment.

The lower uterine segment during pregnancy and the puerperium can structurally be recognized by its thinner decidua, its poverty in glands which are irregular in arrangement, and the loose disposition of its muscular fibers.

Frankl<sup>2</sup> has shown that no decidua compacta but only the loose decidua spongiosa normally develops from the mucosa of the lower uterine segment. And plausibly he explains that such a condition favors the mobility of the lower pole of the ovum, thus facilitating and rendering bloodless the separation of the membranes during the cervical dilatation and descent of the presenting part. Were the union between the ovum and the uterus in this region intimate as, for instance, in cases of placenta previa, every act of labor would be attended by greater difficulty and perhaps greater amount of blood loss than what ordinarily is observed.

Recent studies of the nonpregnant and puerperal uteri confirm the findings of my earlier paper<sup>1</sup> that the cervix after its complete dilatation forms the greater part of the lower uterine segment. From the evidence shown by the specimens, one can only conclude that during labor the cervix becomes elongated as it dilates so that, when it is completely effaced, it constitutes not the minor but the major portion of the lower uterine segment. This may be verified by examining a uterus that has recently delivered a full-term fetus, measuring that portion which corresponds to the isthmus uteri and comparing it with the portion lined by the glistening cervical mucosa as grossly shown by the plica palmatae. Fig. 4 is a diagram of the uterus of a woman delivered by cesarean section who died four hours after the operation. It shows the relative length of the uterine and cervical portion of the lower uterine segment.

That the cervical canal when completely effaced is longer than the uterine portion of the lower segment should not cause surprise; it is but the natural result to be expected; for, in the normal nonpregnant uterus or the involuting puerperal uterus, the cervical canal is also proportionately longer and is almost, and at times more than twice as long as the isthmus uteri.

The above findings cannot sustain the prevailing opinion among modern authors which, according to Williams, holds that the cervix does not lengthen during labor and constitutes not more than 3 or 4 cm. of the lower portion of the fully formed lower uterine segment. Such a picture, however, seems anomalous for it inverts the natural proportion of the two structures, isthmus and cervix, in the nonpregnant uterus.

#### CONCLUSIONS

1. The isthmus uteri begins to be unfolded at the beginning of pregnancy when ovum implantation takes place, to constitute the uterine portion of the lower uterine segment.

2. The upper and lower segments of the uterus manifest recognizable structural differences but their functional differences are manifested during labor.

3. The formation of the lower uterine segment is completed at the end of the first stage of labor when the cervical canal becomes completely effaced.

4. The cervical canal, during labor not only dilates, but elongates. And contrary to the prevailing view, at the end of the first stage of labor the cervix rather than the isthmus takes a larger share in the formation of the lower uterine segment.

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### LEIOMYOMA OF THE BLADDER\*

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WELL-ESTABLISHED instances of leiomyoma of the bladder are rare. De Berne-Lagarde collected thirty-six cases in 1929. In 1931 Kretschmer added twelve cases and published two excellent analytical papers on the subject. We have found ten additional reports of vesicle leiomyoma, which, with the case here reported, increase the total to fifty-nine cases.

S. B., a married, nulliparous Jewish woman of thirty-six years, was admitted to the Gynecologic Service of the Hospital of the University of Pennsylvania Sept. 9, 1933.

The remote history was irrelevant.

Her principal complaints were frequency and difficulty of urination. Frequency, which was first noticed eight years previously, had gradually increased until urination was necessary every half hour. Because walking aggravated the urgency the patient became confined to her home, and during the weeks just prior to hospitalization, to her chair. For several months she had noticed a decrease in the force of the urinary stream, but the flow could be improved by suprapubic manual pressure, a maneuver which finally became essential to urination. She had a sense of incomplete emptying after voiding.

Other symptoms commonly mentioned in bladder wall tumors, incontinence, pain, and hematuria, were absent.

Physical examination revealed a well-nourished woman with no apparent distress or disease. Examination of the head, eyes, ears, nose, mouth, and throat was negative. The lungs were clear and the heart was normal. The blood pressure was 135/90. Abdominal examination was negative except that pressure on the hypogastrium excited a desire to void. The tendon reflexes were normal.

Pelvic examination disclosed normal pelvic organs. In the midline, behind the symphysis, a firm, lemon-sized mass could be felt.

The laboratory reported 4,800,000 erythrocytes, and 9,300 leucocytes per cubic millimeter of blood, 90 per cent hemoglobin (Sahli method), negative blood Wasser-

\*Presented at a meeting of the Obstetrical Society of Philadelphia, May 3, 1934.

mann, blood urea nitrogen 12 mg. per 100 c.c. A catheterized specimen of urine showed abundant albumin, many clumps of leucocytes per high power microscopic field, and occasional erythrocytes. Stains for acid-fast organisms in the urine were negative.

At cystoscopic examination the cystoscope was deflected by a massive protrusion from the left median anterior wall of the bladder. The mucous membrane overlying the mass was normal. The cystoscopic diagnosis was "intrinsic tumor of the wall of the bladder" or "extravesical tumor exerting pressure against the bladder."

A urogram made with intravenous neoskiodan showed a large median filling defect of the bladder, interpreted as due to an intrinsic tumor of the bladder (Fig. 1).

Suprapubic extraperitoneal cystotomy was performed under nitrous oxide and ether anesthesia. The egg-sized tumor could be seen attached by a wide base to the anterior median portion of the bladder just above the internal urethral orifice. The overlying mucosa was incised and the tumor was shelled out with little dif-

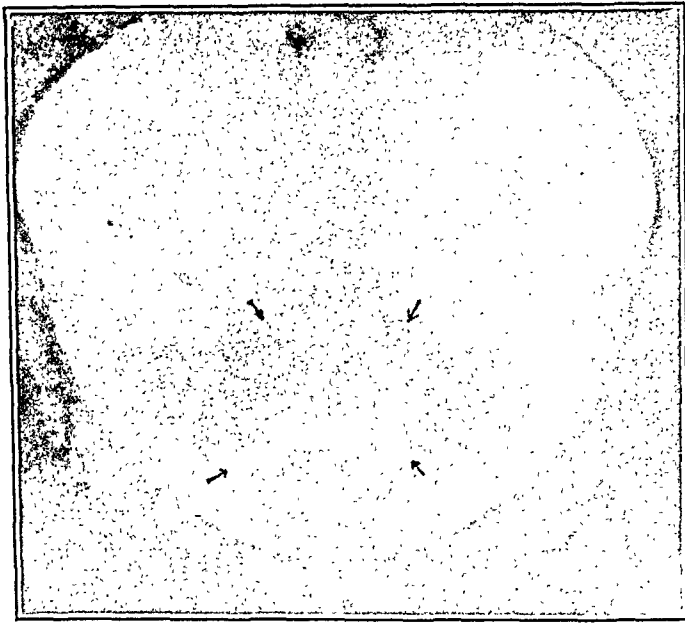


Fig. 1.—Urogram. The arrows point to the filling defect due to the vesicle myoma.

ficulty. An indwelling urethral catheter was inserted and the bladder was closed. The space of Retzius was drained.

Convalescence was uneventful except for a wound infection which prolonged hospitalization. On the twenty-fifth postoperative day the patient was discharged from the hospital with no urinary symptoms. Cystoscopy revealed a healing scar of the vesicle mucosa. Six months after operation the patient reported herself entirely well and symptomless.

*Pathologic Report.*—"The tumor measures 7 by 4 by 3.5 cm. It is encapsulated and the capsule strips with difficulty. The tumor is firm in consistency and there is definite lobulation. The cut surface is grayish white in color and is moist. The appearance is that of fibrous tissue divided into lobules by distinct trabeculae. A considerable number of blood vessels give a vascular appearance to the cut surface. On sectioning the tumor there is an appearance of hyaline degeneration (Fig. 2).

"Histologically, all four sections taken from the tumor show the same general characteristics. In none is any investing epithelium present. The capsule is rather

thin and is composed of muscular tissue. The substance of the tumor is composed of irregular sized whorls between which are trabeculae of dense fibrous tissue. No muscular tissue can be identified in the substance of the tumor. The general appearance is that of a leiomyoma. Many of the cellular elements are compressed. The nuclei, for the most part, are spindle-shaped and take the hemotoxylin stain deeply. They are central in situation. No mitosis is present. The neoplasm is

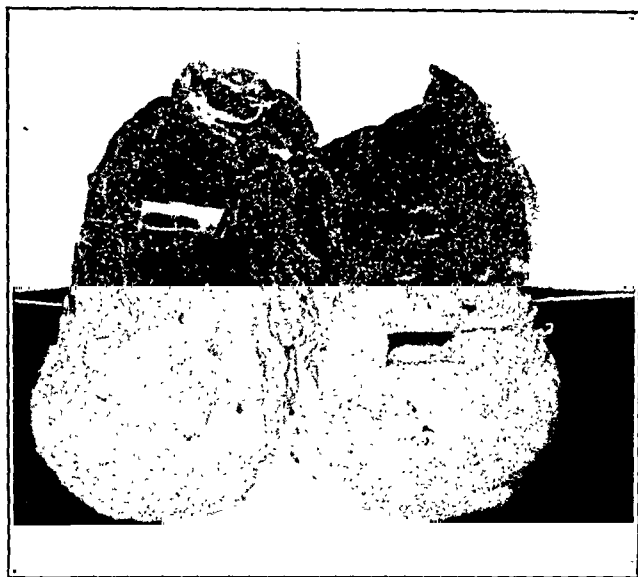


Fig. 2.—Tumor bisected and laid open.

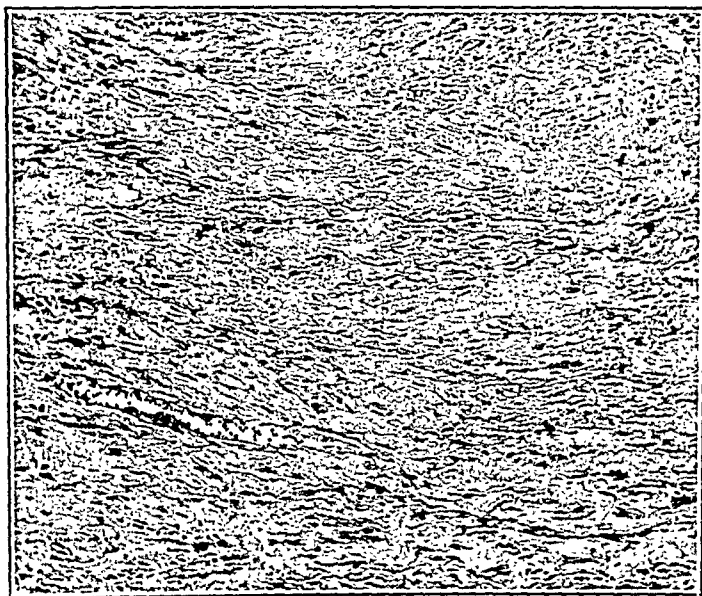


Fig. 3.—Leiomyoma of the bladder. Microscopic appearance.

moderately vascular, and apparently has a peripheral circulation. The tissue is edematous and in some areas shows definite hyaline degeneration. There is no suggestion of malignancy." (Fig. 3.)

After reviewing the literature on leiomyoma of the bladder these facts are apparent:

1. Leiomyoma of the bladder occurs at any age from the second to the seventy-fourth year.



2. It occurs with equal frequency in the two sexes.
3. The growth may vary in size from a microscopic nodule to a mass weighing nine kilograms, and may occur in any portion of the bladder, including the trigone.
4. The tumor may be symptomless; or hematuria, frequency, dysuria, or pain may be present.
5. Diagnosis is made by a three-step procedure: bimanual pelvic examination, cystoscopy and cystography. The most important single finding is normal mucosa covering a tumor of the bladder wall.
6. Vesicle leiomyoma may be mistaken for an extravesicle tumor distorting the bladder, for example, myoma of the cervix uteri, ovarian tumor, or prostatic enlargement.
7. Leiomyoma of the bladder is a benign tumor which manifests itself by mechanical irritation or obstruction, and which may endanger health by favoring urinary tract infection or by occluding the ureter.
8. The treatment is surgical removal.
9. The prognosis is good provided the tumor can be completely removed and provided there is no advanced renal pathology.

## CASES

## CHRONOLOGIC LIST OF CASES PREVIOUSLY REPORTED

- |    |   |   |
|----|---|---|
| 1  | <i>Koll, I. S.:</i> J. Urol. 9: 453, 1923.  |   |
| 1  | <i>Latzko:</i> Ztschr. f. urol. Chir. 13: 85, 1923.                               |   |
| 1  | <i>Smith, E. C.:</i> J. Canadian M. A. 19: 444, 1928.                             |   |
| 2  | <i>Segurolo, Marcelino:</i> Vida Nueva 22: 224, 1928.                             |   |
| 36 | <i>De Berne-Lagarde:</i> Arch. d. mal. d. reins 4: 412, 1929-30.                  | . |
| 1  | <i>Maingot, Rodney:</i> Brit. M. J. 1: 850, 1929.                                 |   |
| 1  | <i>White, E. W.:</i> J. Urol. 26: 253, 1931.                                      |   |
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| 1  | <i>Higgins, C. C.:</i> Ann. Surg. 93: 886, 1931.                                  |   |
| 1  | <i>Krinke, I.:</i> Zentralbl. f. Gynäk. 55: 1556, 1931.                           |   |
| 12 | <i>Kretschmer, H. L.:</i> J. Urol. 24: 575, 1931.                                 |   |
| —  | <i>Kretschmer, H. L.:</i> Trans. Am. Assn. Genito-urinary Surgeons 24: 363, 1931. |   |
| 58 |   |   |

NOTE: Kretschmer's list of 48 cases includes the 36 cases of Berne-Lagarde and in addition the cases of Bohme, Bouchard, Capser, Chamberlain, Gronberger, Kidd and Turnbull, Levings, McNally, Kretschmer, Scholl, Wershub, and Zuckerkandl.

133 SOUTH THIRTY-SIXTH STREET

Fuge, K.: Investigation of the Gastric Acidity in Women with Genital Carcinoma. Monatsschr. f. Geburtsh. u. Gynäk. 97: 37, 1934.

In a series of 80 women who had uterine carcinoma, Fuge studied the gastric acidity according to the Ewald-Boas method. In 115 cases there was anacidity and in 25 additional cases a hypoacidity present. Most of the women in this series had inoperable cancers and had received radiation therapy. Nearly all the women had anemia. The author urges that all women with achylia be treated for this condition because disagreeable symptoms will otherwise arise. He recommends for this purpose a mixture of hydrochloric acid and pepsin.

J. P. GREENHILL.

## THE USE OF FOLLUTEIN IN DYSMENORRHEA\*

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THERE is no need to discuss at length the physical, economic, and social effects of dysmenorrhea and the loss of time and suffering which it causes. It has been relegated to the category of minor gynecologic conditions by the medical profession, but to the individual sufferer it is of major importance. Any method of treatment which will give partial or temporary relief is gratefully received by these patients and should receive attentive consideration by the gynecologist.

Theories as to the etiology of this condition were formerly concerned with mechanical factors to a large degree, and consequently the treatment prescribed was designed to overcome these mechanical factors. As many of these patients present themselves for consideration during their early menstrual life before marriage or childbirth a fair percentage are found to have anteflexed uteri with conical closed cervixes. Dilatation of the cervix with straightening of the anteflexion seemed a logical manner of correcting the supposed abnormality. There have been a sufficient number of good results both temporary and permanent following this treatment for it to have become the method of choice in many of these cases. Many others received only temporary benefit, however, after having been subjected to the trauma and expense of an operative procedure.

Others were advised that their condition must be endured with what help sedatives could afford until after marriage and childbirth when relief might be expected. The relief following childbirth with its growth and hyperplasia of the uterus as well as the dilatation of the cervix which occurs during labor, was assumed to be due to the stimulation of the uterus and the stretching of the cervix. Undoubtedly these factors played some part in the relief afforded, but the endocrine factor involved during pregnancy cannot be ignored as being without some possible benefit.

Without going into a detailed description of the mass of experimental work which has been done in recent years regarding the endocrine physiology of the pituitary and the ovary, we briefly list the presumptive functions and actions of the hormones which they produce as follows: Prolan A from the anterior lobe of the pituitary stimulates follicle ripening, while Prolan B stimulates luteinization. During follicle ripening folliculin is formed which produces growth and vascularization of

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\*Read at a meeting of the Chicago Gynecological Society, April 20, 1934.

the uterus and hyperplasia of the endometrium. In addition folliculin has been shown to stimulate uterine contractions. Progestin, elaborated in the last half of the menstrual cycle produces the secretory or pre-gravid phase of endometrial growth and in addition inhibits further follicle ripening, inhibits uterine contractions and diminishes the renal threshold for the excretion of folliculin.

During pregnancy there is an elaboration of a hormone-like substance, which in the presence of adequate pituitary tissue, will cause follicle ripening, corpora hemorrhagica and luteinization in laboratory animals. If this substance does not remain fresh, the Prolan A-like action fades and the Prolan B-like action predominates, resulting in luteinization and apparent follicle inhibition or arrest of follicle growth. Using an extract from the urine of pregnant women (antuitrin-S), Geist showed a similar effect in the ovaries of women.

In the absence of pelvic pathology and acquired stenosis of the cervix, an endocrine theory of dysmenorrhea has been hypothesized by some observers as follows: Deficient progestin formation, whether primary from insufficient Prolan B or secondary from failure of the ovary to react to its luteinizing effect might result in uninhibited action of folliculin during the premenstrual and menstrual time. This conceivably would result in folliculin stimulated uterine contractions of a painful nature and possibly menorrhagia and clots from a stationary hyperplasia of the endometrium. Another type of imbalance might result from overproduction of folliculin in the presence of an average amount of progestin. Both of these hypothetical hormone derangements might be altered by the administration of a substance which would luteinize and at the same time depress or inhibit follicle activity.

It was the above line of reasoning plus the by-effects of follutein in some cases of abnormal uterine bleeding which prompted this clinical investigation. Two women who had received follutein in an attempt to control menorrhagia reported that in addition to receiving benefit in controlling their profuse menses, that the dysmenorrhea they had previously suffered from was definitely improved. It was decided to administer follutein to a group of patients whose chief complaint was dysmenorrhea, and to survey all patients who had received this substance for other menstrual disorders who had a concomitant dysmenorrhea.

The substance used was follutein, a commercial anterior-pituitary-like substance.\* In most cases the dosage administered was  $\frac{1}{2}$  c.c. intramuscularly daily for five days, making a total of 625 rat units. The time of the menstrual cycle at which this substance was injected was not carefully chosen at first, but subsequent experience seemed to indicate that at least two weeks should elapse from the time the injec-

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\*Prepared from the urine of pregnant women by E. R. Squibb & Sons Co.

tions were started until the menses began, if the maximum effects were to be obtained. Systemic and local reactions were the rule, the deltoid muscle becoming sore, the skin in many instances showing erythema and from six to ten hours after the first injection many patients were chilly, nauseated, and febrile. Subsequent injections gave less local symptoms and practically no systemic symptoms.

An attempt has been made to evaluate the tissue effects on the human ovary of this substance in three cases, using two other cases with very similar findings as controls. Two colored patients, one twenty-two and the other twenty, both married, one having had a supposed early abortion some years before, both having been previously curetted, gave a history of irregular and prolonged menstruation since the onset at puberty. An attempt was made to control the bleeding of one patient with follutein but after six weeks' amenorrhea the condition returned and a second course failed. A third course was given just prior to operation (ten days). The other patient received no treatment. Both were flowing at the time of operation at which time bilateral polycystic ovaries were found, the cysts being about navy bean size. Two cases of uncomplicated uterine fibroids with regular menstruation were treated ten days before operation and the operation performed on one, one week before the next period was expected and on the other just at the end of menstruation. The fifth patient was not injected but was also operated upon for uncomplicated fibroid uterus at the end of menstruation. The slides of the ovaries seem to show more interstitial vascularity and perifollicular and intrafollicular hemorrhage in those cases receiving follutein. The effect on the granulosa cells and the theca interna cannot be accurately evaluated from such a small number of cases but these changes conform to those described by Geist in cases treated with a similar preparation. It is impossible to determine the significance of these apparent changes.

Thirty-nine patients have been treated with follutein and reports of one month or more have been obtained. A detailed analysis of these cases individually is appended. They have been classified into three groups according to clinical types and as to whether they presented other menstrual disorders. The results have been encouraging as a number of patients in each group received substantial relief. The duration of the relief in many cases is as yet unknown as insufficient time has elapsed since treatment to determine whether the symptoms will return or whether the relief will be permanent. The group of patients with no associated menstrual disorder who were clinically feminine in type have received only one course of treatment, and those benefited have as yet had no recurrence.

No attempt was made to alter other possible etiologic factors which might augment or aggravate the dysmenorrhea. The psychic effect of

TABLE I. NO ASSOCIATED MENSTRUAL DISORDER, PERIODS REGULAR, PATIENTS CLINICALLY FEMININE IN TYPE

NO. CASES	GOOD RESULT	FAIR RESULT	NO EFFECT
10	5	2	3
Average duration	3½ mo. (1-6 mo.)	3½ mo. (2-5 mo.)	(2 definitely neurotic)
Percentage	50	20	30

TABLE II. CASES ASSOCIATED WITH DELAYED, IRREGULAR AND SCANTY MENSES AND PERIODS OF AMENORRHEA

	NO. CASES	RESULT			RECURRENCES	REMARKS
		GOOD	FAIR	NONE		
Pituitary type	7	5	2		1 after 8 mo. good result	
Feminine type	10	6	3	1	1 after 6, 1 after 3 mo. good	1 case failure suspect cervical stenosis
Hypothyroid type	1		1			
Total	18	11	6	1		
Average duration		4 mo. (1 to 8)	3½ mo. (2 to 5)			
Percentage		61	33	6		

TABLE III. CASES ASSOCIATED WITH MENORRHAGIA AND FREQUENT MENSES

	NO. CASES	GOOD	RESULT SLIGHT	NONE	RECURRENCES	REMARKS
Feminine type	9	4	3	2	1 good after 6 mo. and 1 after 4 mo.	1 failure neurotic. 1 failure suspect incomplete abortion
Average duration		8 mo. (2-12)	6 mo. (2-12)			
Percentage		44	33	22		

these injections cannot be accurately evaluated. The first few patients were frankly told that the procedure was experimental, could do no harm, and might be beneficial. Later as the results began to appear, other patients were told that some relief might be expected. Some of these have continued through several periods with alleviation of symptoms.

Because of the encouraging results from this treatment in a fair proportion of cases the following conclusions have been drawn:

1. Certain cases of dysmenorrhea may have an endocrine basis.
2. Luteinizing substances may give partial or almost complete relief, the duration of which is as yet unknown.
3. These substances deserve a trial in the absence of pelvic pathology, particularly in patients of the feminine type where there is no associated menstrual disorder, before recourse is had to surgical procedures or irradiation therapy.

## SEXUAL EXCITABILITY AS RELATED TO THE MENSTRUAL CYCLE IN THE MONKEY

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(*From Carnegie Institution*)

SEVERAL systematic attempts have been made to determine cyclic changes in the sex desire of women. The methods employed in these studies (Stopes,<sup>1</sup> Davis,<sup>2</sup> Hamilton<sup>3</sup>) lack the objectivity desirable in a scientific study and the results are further vitiated by the inaccuracies of memory on the part of the subjects. Moreover, the most important event in the menstrual cycle, namely ovulation, is at present not ascertainable with accuracy in women.

Inasmuch as the important events of the cycle can be readily determined in favorable female rhesus monkeys and since their sexual physiology in all essential respects seems to parallel that of women (Corner,<sup>4</sup> Allen,<sup>5</sup> Hartman<sup>6</sup>), this animal seemed a promising subject for studying certain aspects of sex behavior and its physiologic basis. A first step in such a study has been made by correlating quantitative changes in sex desire with the physiologic events of the menstrual cycle.

Sexual excitability was measured by recording the frequency with which certain sexual elements of the female's behavior occurred when she was mated successively to each of four different males for periods of ten minutes. The three behavioral units chosen for this measurement were: (1) "presenting"; (2) attempts to attract the male's attention by threatening an outsider; (3) going toward as against going away from the male. The first two are obviously sexual behavior and they are reacted to as such by the male. The third shows some correlation with them and was therefore considered to be an indication of sex desire.

Eight females have been studied for from three to eight months each. Tests were made three times a week. The sexes were kept segregated except during the tests.

The physiologic changes in the sex tract were followed by means of vaginal smears and rectal palpation of the uterus and ovaries.<sup>6</sup> In the cases here reported, therefore, the exact time of ovulation is known.

Primates differ from the lower mammals in accepting copulation throughout the cycle instead of for only a short period at the time of ovulation. The present observations indicate, however, that sexual excitability typically increases just before ovulation and falls thereafter, even though the drop is not usually so complete as to mean consistent refusal to mate.

This relationship between sex desire and ovulation is shown graphically in Fig. 1, where sex desire scores are plotted against the number of days before and after ovulation, which event is indicated by the vertical line down the center of the chart. Each curve represents one cycle, from the first observation after the beginning of menstruation to the last test before the succeeding period.

The cycles shown in this chart have been chosen from all the cycles studied as being the only ones where the behavior was obviously satisfactorily measured and ovulation was definitely determined. There were many cycles in which the animals did not ovulate, some in which ovulation was not determined with certainty, and a few in which ovulation was ascertained but behavior did not change. We cannot be sure

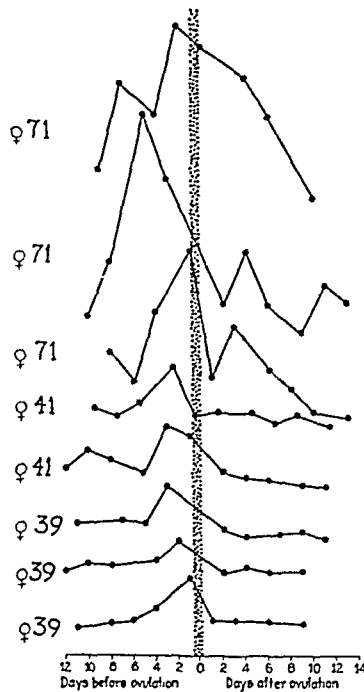


Fig. 1.—Rise and fall of sex desire in the menstrual cycle of the monkey. Six cycles plotted from the day of ovulation.

that sex desire was measured under the most favorable circumstances in these cases. The purpose of the present paper is to report only the typical picture. Exceptions to the rule will be discussed later after more cases have been studied.

As Tinklepaugh<sup>7</sup> has pointed out, this rise before ovulation is what is to be expected on the basis of the relation of estrus to ovulation in those animals which have a limited mating period. He found that a pair of chimpanzees copulated only during the time of swelling of the sex skin of the female which, however, in that animal extended over the greater part of the cycle after the menstrual flow had ceased. Zuckerman<sup>8</sup> reports that male baboons show a preference for females with swollen sex skin and that the females in this condition stayed close to their males, presenting frequently. The swelling of the sex skin in certain primates is roughly associated with ovulation.

Comparing the curve for the monkey shown in Fig. 1 with the curves of sex desire reported for women (Stopes, Davis, Hamilton, Tinklepaugh), it is to be noted that the premenstrual rise reported for women is entirely absent in the monkeys. This fact raises the question, "Are women different or have the answers they have given investigators been about something more complex than what we have measured in the monkey?" Tinklepaugh<sup>7</sup> has suggested that affection is a complicating factor in the human. There may be others. We suggest that a more precise definition and an effort to analyze the factors influencing sexual excitability in women should perhaps be the next step in trying to obtain information from human subjects about the trait we have measured in monkeys. We define this trait as the amount of sex response that is elicited by a relatively constant stimulus. A similar definition that would be better suited to human conditions might be the amount of stimulation necessary to bring out a relatively constant response, such as local glandular secretion or orgasm. However, whatever definition of sexual receptivity is considered suitable, it is hoped that the objective method it has been possible to use in the study of monkeys may help to define the problem in further investigations of sex responses in women.

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Day, Hilbert F.: Uterine Bleeding From a Needle in the Uterine Cervix, New England J. Med. 211: 29, 1934.

Slight uterine bleeding in a woman fifty-seven years old. Had three operative deliveries and in interval between second and third a plastic operation on cervix and perineum. On suspicion of malignancy (without preceding curettage) a vaginal hysterectomy is performed. As cause of the hemorrhage is discovered the rusty part of a surgical needle undoubtedly lost during the cervical repair but not displaced by the subsequent third delivery which had occurred twenty-two years before this hysterectomy.

HUGO EHRENFEST.



# OVARIAN RESPONSE IN MONKEYS (*MACACUS RHEBUS*) TO INJECTIONS OF ANTUITRIN-S

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HISAW<sup>6</sup> and others have shown that subcutaneous injections of an aqueous pyridine extract of the anterior pituitary produce a marked follicular response in the ovaries. We have been able without difficulty to verify this statement with respect to *Macacus rhesus*. It has been assumed by others that similar effects would be induced by the injection of extracts of pregnancy urine. In other words, do these so-called anterior pituitary-like substances isolated from pregnancy urine produce changes in the ovary similar to those produced by extracts of the gland itself?

Engle working with rodents in 1929<sup>3</sup> and with monkeys in 1933<sup>2</sup> concluded that the changes were not similar. The work of Schoekaert,<sup>8</sup> Evans, Meyer and Simpson,<sup>4, 5</sup> Leonard,<sup>7</sup> and Smith and Leonard<sup>9</sup> also substantiate this conclusion.

Recently antuitrin-S and other similar preparations have been advocated by certain clinicians as a means of controlling functional bleeding from the uterus, a control thought originally to be brought about by the stimulation of luteinization of the follicle. We were interested to learn the effect of this extract upon the ovaries of the *Macacus rhesus*, and accordingly, varying doses were administered in the following way to five mature and one immature animal:

Exploratory laparotomies were performed upon Macaques 38 and 40 weighing 5,045 and 4,935 gm., respectively, upon July 8, 1932. At this time the ovaries were measured and observations of the character of their external surfaces were recorded. Beginning July 22 and continuing until August 3, each animal received daily subcutaneous injections of 200 R. U. of antuitrin-S, until a total of 2,400 R. U. had been administered. On August 3 a second laparotomy was done, and the left ovary was removed. Serial microscopic sections of these ovaries were studied but no morphologic change in the follicles was noted.

Macaques 13 and 34, weighing 5,330 and 5,540 gm., respectively, had been in the laboratory for six months and during this time a complete menstrual record had been kept. On Aug. 6, 1932 the left ovary of each animal was excised as a control. Observations and measurements of the right ovaries were likewise made. Beginning the following day each animal received 200 R. U. of antuitrin-S subcutaneously daily for two weeks, a total dosage of 2,800 R. U. On August 20 exploratory laparotomies revealed no gross changes in the remaining ovary in either animal. The right ovary of Macaque 34 was removed for histologic study. Comparison of serial sections of this ovary with serial sections of the left ovary previously

removed as a control showed no follicular changes corresponding to those produced by the subcutaneous injection of aqueous pyridine extracts of the anterior lobe.

It was then decided to test the effect of much larger doses of antuitrin-S. M. Rh. 36 weighing 7,795 gm. and whose menstrual history had been followed for seven months was chosen as a suitable animal. Beginning Nov. 23, 1932, 450 R. U. were injected twice daily until December 5, when a total dosage of 5,400 R. U. had been given. On December 5, or fourteen days later, the uterus, both ovaries and the fallopian tubes were removed for histologic study. Aside from a very slight or questionable cystic degeneration of the follicles and the presence of fewer mitotic figures, these ovaries upon microscopic examination differed in no way from those of a so-called normal ovary.

Hisaw<sup>6</sup> and Diddle<sup>1</sup> experimenting with sexually immature female monkeys, found that following the subcutaneous injection of an aqueous pyridine extract of the anterior pituitary, the ovaries increased to eighteen times normal size and contained enlarged follicles. It was of interest therefore to determine whether corresponding changes could be produced by the subcutaneous injection of relatively large doses of antuitrin-S. For this experiment an 1,800 gm. animal, M. Rh. 31 that had been in our colony for over a year, was used.

On Nov. 4, 1932, an exploratory laparotomy was done under nembutal and ether anesthesia, and measurements of the uterus and ovaries were made. Beginning Nov. 16, 1932, 300 R. U. of antuitrin-S were injected subcutaneously at 9:00 A.M. and 5:00 P.M. daily until November 22, when a total dosage of 3,600 R.U. had been given. On that day an exploratory laparotomy showed no gross changes in the uterus or ovaries. Beginning the following day (November 23) these injections (300 R. U. antuitrin-S at 9:00 A.M. and 5:00 P.M.) were repeated daily until December 6, when a total of 10,800 R. U. had been administered. A laparotomy on this day revealed no gross changes in the ovaries or uterus. However, the right tube and ovary were removed for histologic study which proved negative.

From December 19 to and including December 27 the animal was given 150 R. U. at 9:00 A.M. and 5:00 P.M. daily. From December 28 onward, antuitrin-S was administered in the following sequence: Upon December 28 and 29 100 R. U. were given intravenously and 200 R. U. subcutaneously. Upon December 30 and 31 300 R. U. were injected directly into the heart. From January 1 to January 5 this dose was increased to 500 R. U. daily. Only a moderate reaction followed these intracardiac injections.

Upon January 6 following a total dosage of 16,500 R. U. the animal was killed. Grossly, the remaining left tube and ovary were normal and these findings were confirmed by the study of microscopic sections.

#### CONCLUSIONS

1. In the case of four mature *Macacus rhesus* monkeys, the daily injection of 200 R.U. of antuitrin-S to a total dosage of from 2,400 to 2,800 R.U. produced no histologic evidence of luteinization of the follicles of the ovary.

2. The injection into a fifth mature animal of 450 R.U. daily to a total dosage of 5,400 R.U. gave correspondingly negative results.

3. The injection into an immature animal of varying doses of antuitrin-S over a period of two months, at the end of which period 16,500 R.U. had been administered, produced no microscopic evidences of luteinization of the ovarian follicles.

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## SIMULTANEOUS BILATERAL TUBAL PREGNANCY

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COMPARATIVELY few authentic cases are reported in the literature in which simultaneous bilateral tubal pregnancy occurred.

Paul Bloch cited fifty-seven cases, the first having been reported in 1890. Schochardt, reporting a case in 1928 quotes Cheval as stating that there are only sixteen authentic cases on record, while Meyer in 1931, reviewing the literature, reports twenty-eight authentic cases. F. D. Johnson reported one other case in 1932.

The case reported herein is of special interest in that:

1. The patient had no premonitory manifestations suggesting ectopic pregnancy prior to her initial attack.
2. Tubal abortion of one tube and ruptured tubal pregnancy of the other tube.
3. Histologic corroboration of the surgical findings.

Mrs. M. M. (No. 04913), white, aged thirty-eight years, was admitted to the Brooklyn Women's Hospital on Oct. 23, 1933, with a history of having experienced, eight hours previous to admission, a sudden stabbing pain in the lower abdomen accompanied with vomiting which caused her to faint. This acute pain in the abdomen had radiated to the left shoulder. She fainted four or five times after the initial attack and could not sit up in bed on account of the pain and dizziness.

Catamenia began at the age of thirteen years, every twenty-eight days, lasting four to five days, last period Aug. 12, 1933. Married thirteen years. Two normal spontaneous deliveries, twelve and nine years previously. Spontaneous abortion five years ago followed by curettage for bleeding, with no apparent sequelae.

*Physical Examination.*—Patient in shock; pulse small, thready, 140; respiration 30; temperature 100° F. The heart and lungs negative. Abdomen tense and rigid, with greatest spasticity in the R. L. Q. There was a bluish discoloration around the umbilicus (Cullen's sign).

*Vaginal examination:* No bleeding, cervix pointing downward, very tender to touch and on motion, fullness and boggiess in the right fornix extending posteriorly into the culdesac which was also tender to touch. The size of the uterus could not be made out on account of spasticity of the abdominal muscles. Impression at this time was that of a ruptured ectopic.

*Operation.*—Free and clotted blood was found in the abdominal cavity and posterior culdesac. Uterus enlarged and soft. Right tubal abortion with a clot ex-

tending well into the frimbriated portion. Left tubal rupture situated about one-eighth of an inch away from the cornual junction of the uterus (Fig. 1). Ovaries were small with corpus luteum of pregnancy in left ovary.

Right salpingectomy and left salpingo-oophorectomy with ventral suspension of the uterus were performed. Transfusion of 700 c.c. of Type 2 (Moss) whole blood from family donor was given at the time of operation with no immediate reaction.

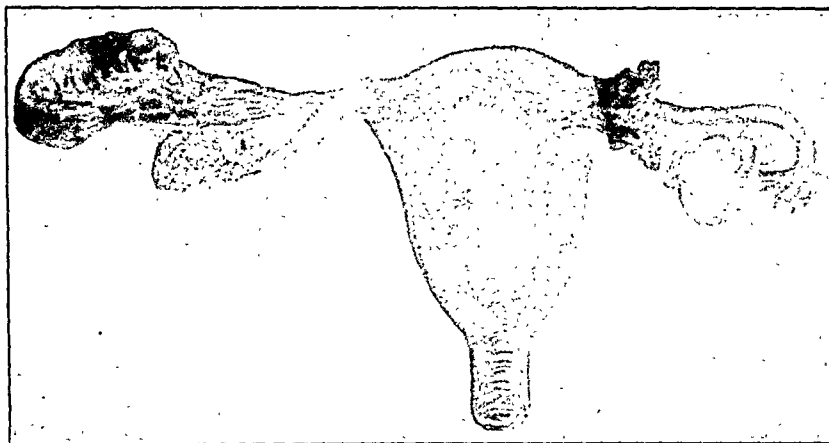


Fig. 1.

Fig. 1.—Showing tubal abortion of right tube rupture of left tube.



Fig. 2.

Fig. 2.—Section of the vicinity of the defect shows decidua and partly necrotic chorionic villi invading the wall of the tube.



Fig. 3.

Fig. 3.—Section of the right tube shows blood clot with chorionic remnants, indicating the abortion of the tubal pregnancy.

*Pathologic Report* (Dr. Goldzieher).—Right tube was of practically normal appearance and caliber with the exception of the terminal portion. About 2 cm. of the latter showed swelling which included the frimbriated end of the tube. The swollen portion was dark red in color, the wall was distended and the lumen filled with a massive coagulum.

The other tube was of normal appearance throughout, except for the medial portion close to the uterus. This portion showed a fairly large defect with ragged edges, while the remnants of the tubal wall were considerably thinned out. Microscopic examination of the vicinity of the defect showed decidua and partly necrotic chorionic villi invading the wall of the tube (Fig. 2).

Microscopic section of the other tube showed blood clot with a few chorionic remnants, indicating the abortion of the tubal pregnancy also in this tube (Fig. 3).

The ovary showed a definite corpus luteum of pregnancy (Fig. 4).

On the third day postoperative temperature reached 101° F., but was otherwise normal throughout. On the fourth day postoperative, respirations became very

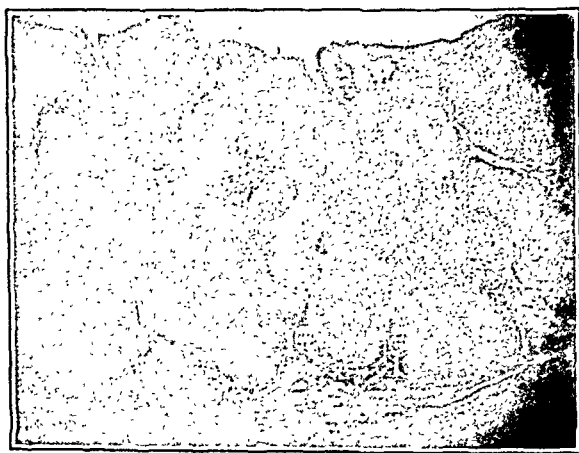


Fig. 4.—Section showing corpus luteum of pregnancy.

rapid and labored with dilated ala nasi but temperature remained low. Examination of the chest showed a massive collapse of the right lung. This responded very readily to treatment of CO<sub>2</sub> and O.

The patient was discharged on the fourteenth day, with the following note: wound healed by primary union. Temperature, pulse, and respiration normal. Blood pressure 118/70. All signs in chest clear. No vaginal bleeding.

On Dec. 21, 1933, abdominal scar was firm. Patient menstruated on December 7 for three days, no clots. Vaginal examination showed the cervix in the axis of the vagina. Uterus anterior. No pelvic tendernesses or masses palpated. Chest clear. Blood pressure 140/92. Hg, 80 per cent.

## LOCALIZED TRAUMATIC CYANOSIS IN THE NEWBORN

J. H. TELFAIR, M.D., AND J. A. GAINES, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics, Fordham Hospital)

TRAUMATIC cyanosis is a relatively rare entity. There are approximately 143 reported cases, which moreover, as far as we have been able to ascertain, do not include a single occurrence in the newborn. The condition per se is extremely spectacular and has made an indelible impression on the minds of those who have had the opportunity to view this picture following the crushing trauma of machine, vehicle or panic-driven mob. We submit the report of a case with necropsy findings, in which this phenomenon resulted as a complication of labor. We shall first present, however, a review of the salient features of traumatic asphyxia or cyanosis with special reference to its pathogenesis.

Traumatic asphyxia refers to a localized, deep cyanosis of the face and neck which immediately follows a sudden compressing force exerted upon the thorax or abdomen. The picture is striking not only because of its unusual distribution but also because of the characteristic discoloration which is livid blue, purple, or blue black. Minute ecchymotic spots or petechial hemorrhages are usually present. The discoloration begins to fade in two to four days and often disappears within two to three weeks, without, however, the color exhibiting the changes of tint usually seen following subcutaneous hemorrhages. The area of involvement is not always confined to the face and neck. Sometimes it extends as far as the third rib anteriorly and posteriorly along the shoulders to the lower level of the trapezius muscles. The reported cases followed for the most part a crushing injury in panics or direct compression by machines. The force need only be exerted for a few seconds to a few minutes, and often except for abrasions and contusions have not caused any apparent injury of the chest wall, lungs, heart, or mediastinal structures. Of course from the nature of the etiology there may be concomitant and sometimes fatal injuries, but the majority of reported cases recovered, and those that did not succumbed apparently to the more serious associated injuries.

Perhaps the nearest approach to the case to be reported is that described by Kredel.<sup>1</sup> "An infant only seventeen hours old presented an umbilical hernia containing the whole liver and the greater part of the intestines. Great pressure had to be exerted upon the liver to reduce it into the abdominal cavity and great force was necessary to close the abdominal wall. At the end of the operation, the child's face showed a deep blue discoloration marked by numerous petechial hemorrhages. It was his opinion that the pressure exerted upon the liver caused a large mass of blood to flow into the right heart and that this pressure was communicated to the face and neck."

*Case Report.*—On the twenty-first of December, 1933, Mrs. L. D., thirty-seven years of age, gravida x, para vii, gave birth to a nine-pound twelve-ounce male infant. Her pregnancy had been uneventful except for a moderate hypertension and albuminuria on admission. The entire labor lasted for seven hours. The second stage was estimated at forty-five minutes. The labor pains at the time of delivery were extremely weak. Delivery of the head required the aid of Kristellar expression. There was some difficulty and delay in delivering the shoulders.

<sup>1</sup>Kredel: *Zentralbl. f. Chir.* 34: 1472, 1907.

At birth the infant showed marked finely mottled, purple cyanosis of the face and neck and moderate cyanosis of the extremities. Though there was no evidence of vaginal or perineal laceration, bright red blood was aspirated from the pharynx. A small amount was also expressed from the nose. The cry was weak. The cyanosis of the hands and feet disappeared but that of the face remained a deep purple blue with numerous small petechial hemorrhages. The conspicuous contrast between this unusual localized and demarcated discoloration of the face and the rest of the body simulated in every way the colorful pictures of traumatic cyanosis seen in adults. Soon the usual indications of cerebral hemorrhage made their appearance including general apathy, weak, high-pitched cry, feeding difficulty, increased respiration and bloody spinal tap. Irregularly at first and more persistently near terminus, the extremities also showed moderate cyanosis, *but the following observation showed not only that this cyanosis was part of the cerebral picture and entirely distinct from the traumatic cyanosis of face and neck, but also that cyanosis can be caused, on the one hand, by a decrease in oxygen content of the blood, and on the other hand, by persistent venous dilatation. When CO<sub>2</sub> (7 per cent) and O<sub>2</sub> (93 per cent) was administered to the infant the entire body assumed a rosy hue but the head and neck remained as purple as it had ever appeared before.* The child lived for a few days. Postmortem examination, performed by Dr. Louis Ferrara, showed no injury to the thoracic or abdominal organs. The right heart seemed slightly more enlarged than normal. There were no congenital cardiac abnormalities. The lungs were not atelectatic. The thymus was not abnormally enlarged and there was no occlusion or pressure upon the innominate or internal jugular veins. The veins of the neck were dilated. Examination of the brain showed slight cerebral congestion, a subtentorial hemorrhage and a dilated right-lateral ventricle. Section of the skin of the face revealed dilatation and engorgement of the vessels but no extravasation of blood into the skin.

#### CONCLUSIONS

We present this case as the first instance of traumatic cyanosis in the newborn to be reported as far as our investigations have permitted us to discover. We believe that the compression encountered in the delivery of a ten-pound baby aggravated by dystocia due to shoulders was the causal factor.

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### SEPTICEMIA IN THE NEWBORN\*

WALTER B. MOUNT, A.B., M.D., F.A.C.S., MONTCLAIR, N. J.

(From the Department of Obstetrics, Mountainside Hospital)

THE patient's first pregnancy terminated in the birth of a normal child eight years previously. In this second pregnancy there was no evidence of toxemia and the gain in weight was less than twenty pounds. Three weeks before delivery the mother received a slight injury of the abdomen which caused very little pain and of which she thought no more at the time.

Delivery at term occurred on Feb. 7, 1933, in Mountainside Hospital and was spontaneous, labor lasting less than twelve hours. The membranes ruptured in the second stage. Because of uterine inertia late in the second stage one minim of pituitrin was administered with good results. A deep median perineotomy was done, so that the baby's head was not subjected to long pressure on the perineum. The

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\*Presented at a meeting of the New York Obstetrical Society, May 8, 1934.

baby weighed 7 pounds and 14 ounces and was clinically normal. For a number of days after birth there were a few transitory skin lesions which were not noteworthy. He nursed well. The initial loss of weight was 9 ounces and then he began to gain slowly. On the eighth day he was circumcised; four sutures of 00 plain catgut were used, and the wound healed with no evidence of infection. On the eleventh day he weighed 7 pounds and 7½ ounces and seemed well in every way; the cord stump was clean and dry but had not dropped off; the circumcision wound was healing. He was allowed to go home with the mother. On that day the nurse developed a coryza and wore a mask over mouth and nose whenever handling the baby.

Early on the twelfth day it was noticed that the left arm moved not as freely as the right. That afternoon there developed a fusiform swelling of the left upper extremity with its midpoint slightly above the elbow. There was redness of the skin, local heat, pain when the arm was touched or moved, and a petechial spot the size of a pinhead on the anterior surface of the elbow. The left axillary glands were enlarged. There was a slight rise of temperature. The baby had a very good day and slept most of the time except when nursing. Wet dressings were applied to the arm. During the night the baby was somewhat wakeful and restless and there was a transitory strabismus.

By morning the swelling had increased. A blood examination showed no anemia, 8,400 leucocytes and 89 per cent polymorphonuclears. The urine had a faint trace of glucose and a marked trace of albumin (4-plus). A blood culture was taken. During this day, the thirteenth, he nursed very well until three o'clock. By that time the liver had definitely increased in size, the swelling and induration of the arm extended to the shoulder and the axillary glands were larger. There was some abdominal distention, and a number of small green stools and some gas were passed. Ten cubic centimeters of the mother's blood was given intramuscularly. Later there was vomiting several times of small amounts of clear fluid. The abdomen became markedly distended. The general condition and color grew worse. There was a constant grunting respiration. There was no bulging of the fontanel, no rigidity of spine or extremities, and no increase of deep tendon reflexes. There was no jaundice. There was very slight fever.

A surgeon saw the patient with the pediatrician. The peritoneal cavity was aspirated and clear, thin, yellow fluid obtained. Two incisions were made over the upper and outer part of the arm where fluctuation seemed greatest, but no pus was evacuated. The baby grew worse rapidly. He was readmitted to the hospital, and was given glucose intramuscularly, abdominal stupes, minim doses of pituitrin, a colon irrigation and carbon dioxide in oxygen. He grew weaker and died forty-five hours after the first symptom had been noticed.

The mother remained well.

Autopsy report: No eruptions. Heart, gastrointestinal tract, kidneys, brain, and meninges normal. Several dark red consolidated areas scattered throughout both lungs; stage of red hepatization. Peritoneal cavity contained considerable clear yellow fluid. Liver dark in color, enlarged and engorged with blood. Spleen somewhat enlarged and congested. Two incised wounds of upper outer part of left arm. Region of left elbow and arm swollen and the skin over this area dark red. The region of the left elbow was opened by a linear incision. When the deeper tissues were reached considerable creamy yellow pus escaped from an abscess cavity which communicated with the elbow joint and extended upward about 2 inches. The lower end of the humerus showed roughening with destruction of cartilage. Circumcision healed. Section through umbilicus showed no evidence of infection or thrombus formation. Culture from peritoneal fluid aspirated before death developed no growth. Blood culture positive for hemolytic staphylococcus.



Pathologic diagnosis: *Staphylococcus (hemolytic) septicoemia*. Bronchopneumonia. Contributory cause of death: Abscess of left elbow joint and adjacent soft parts.

Only 69 cases of proved septicemia in the newborn have been reported. Of these Dunham<sup>1</sup> had 39 cases in a five-year period in one hospital; some of these cases were recognized only because blood cultures made during life or taken from the heart blood immediately after death were routine in all cases of unexplained illness in the newborn. Since Dunham's excellent paper with bibliography appeared early in 1933 four cases<sup>2, 3, 4, 5</sup> have been published, but Dr. Dunham<sup>6</sup> reports that there have been twelve additional cases on the Pediatric Service of the New Haven Hospital. In a five-year period there were over 3,000 births in that hospital with an incidence of eight cases of proved septicemia, the other 31 patients having been delivered elsewhere. In Dunham's 39 cases osteomyelitis occurred four times.

As obstetricians we are interested in the newborn, even though we may give to the pediatricians the entire responsibility for their welfare. This case is reported so that we shall have blood cultures taken in obscure or serious illnesses in the newborn. When *Staphylococcus albus* is reported, repeated cultures should be taken because it is a frequent contaminant. Ultimately more helpful knowledge may result. In treatment repeated blood transfusions should be used.

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## ENDOMETRIOSIS, CHRONIC BARTHOLINITIS, AND OVARIAN CYST\*

CHARLES EDWIN GALLOWAY, M.D., EVANSTON, ILL.

THE patient, Mrs. C. R., a widow, aged twenty-nine years, presented the following history: Two labors, both full-term and normal deliveries in 1923 and 1924. Pelvic laparotomy nine years ago at Cook County Hospital, apparently for salpingitis and both tubes and one ovary were removed. Several Bartholin abscesses required incision and drainage. Following the laparotomy the incision did not heal properly and the patient states that from then on for six years at each menstrual period, bleeding took place from the small raised area, which now resembles a mulberry, in the middle of the incision. She also states that there has been considerable pain in the abdominal wall with each menstrual period. For the past three years, however, she has been free of the bleeding from the abdominal wound but the pain has persisted and is quite severe. It starts a day or two preceding the period and lasts a day or two after the period is over. Her chief complaint at the present time is lower abdominal pain which is almost constant. She denies having any fever.

Examination revealed a small mulberry-sized mass half-way between the pubis and the umbilicus, and underneath this was a mass approximately 5 cm. in diameter, very hard and very tender which seemed to be connected with the body of the uterus.

\*Presented at a meeting of the Chicago Gynecological Society, May 18, 1934.

The vagina was normal except for a scar on either side corresponding to the location of the Bartholin gland. The cervix was not eroded. The vagina was filled with a purulent discharge. The uterus was held firmly against the abdominal wall, with a soft cystic mass to the right and posterior. Nothing could be palpated on the left side.

The Wassermann and Kahn tests were both negative; temperature normal over a period of thirty-six hours that the patient was observed prior to operation; white blood cells 17,500.

*Diagnosis:* Endometriosis; chronic Bartholinitis; probable ovarian cyst.

*Operation:* May 17, 1934. Drop ether anesthesia. A midline incision was made from the pubis to the umbilicus, including the old incision. The mass described in the anterior abdominal wall was found as expected, adherent to the body of the uterus. The same process had also extended toward the bladder. The left ovary and tube were absent and the right tube was absent. The right ovary was about the size of a lemon and was entirely cystic.

The omentum was adherent to the abdominal wall and to the pelvic viscera. With slow dissection the entire pelvic contents were freed and the right ovary together with the fundus of the uterus and the mass described, still adherent to the anterior abdominal wall, were removed intact.

The raw surfaces were then peritonealized with No. 2 plain catgut and the abdomen was closed in the usual manner using four black silk stay sutures. Before leaving the operating table the patient was given a quart of normal salt solution at 110° per rectum.

On Dec. 17, 1934, the patient was well, the incision showed no evidence of endometrial deposits, and there were no pelvic symptoms.

#### PATHOLOGIST'S REPORT

Microscopic sections taken from the firm mass just beneath the skin surface showed the following: In one area small tubule and duct-like structures composed of columnar epithelium and surrounded by masses of small, dark spindle-shaped cells and lymphocytes, were scattered unevenly through the mass of coarse, dense, fibrous, connective tissue. Some of the tubules were dilated to form cyst-like structures and contained red blood cells and lymphocytes. Several of these epithelial structures with their dense cellular stroma had a striking resemblance to fundic endometrium. Another part of this tumor mass consisted of atrophic ovarian tissue. Its stroma contained a small mass of atypical epithelial elements embedded in a stroma which was more cellular than the ovarian stroma elsewhere. Imperfect alveolar and tubular structures were formed by the epithelial elements but, while these were greatly distorted, definite evidence of anaplasia was lacking.

*Diagnosis:* Endometrioma of the abdominal wall. Unilocular serous cystoma of one ovary. Chronic fibrous perimetritis and perioophoritis.

## CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MAY 18, 1934

The following case reports and papers were presented:

Endometriosis, Chronic Bartholinitis, and Ovarian Cyst. Dr. C. E. Galloway.

(See page 128.)

The Management of Pregnant Women With Heart Disease. Dr. J. E. Fitzgerald. (See page 53.)

Labor in the Cardiac Patient. Dr. R. A. Reis and Dr. L. E. Frankenthal, Jr. (See page 44.)

## American Gynecological Society

## Fifty-Ninth Annual Meeting

White Sulphur Springs, W. Va., May 21, 22, 23, 1934

(Continued from December issue.)

9. Blood Chemistry in Preeclampsia and Eclampsia. Drs. H. J. Stander, and J. F. Cadden, New York City. (See page 856, December, 1934, issue.)

## DISCUSSION

DR. PAUL TITUS, PITTSBURGH, PA.—This paper attempts to correlate general blood chemistry findings with treatment in eclamptic toxemia. Obviously the idea of repeated analyses by which changes may be an index of the progress of the disease, is a practical one in which the laboratory can actively assist the clinician.

I agree that preeclampsia and eclampsia is the same disease, with the mere addition in the latter of a single spectacular symptom—the convulsion, but also that *all* toxemias of pregnancy are etiologically and clinically related. There is considerable evidence to support this view.

Dr. Stander has done something quite new in his analysis and evaluation of glutathione and thioncine values. The functions of these compounds are obscure and while his results were negative, it is well that this fact has been settled. Messer of the Oliver Research Laboratory in Pittsburgh believes, however, that it is a mistake to name these nonfermenting “blood sugar” fractions “saccharoids” because they are not sugar-like but are sulphur compounds.

Stander makes a useful clinical application of progressive changes in the  $\text{CO}_2$ -combining power, and the blood uric acid namely, that a continued low level, or a decline in  $\text{CO}_2$ -combining power, with a steady increase in blood uric acid warrants active therapeutic treatment and surgical interference. The significance of uric acid increase may be speculative without impairing the therapeutic importance of this observation.

This paper finds us still somewhat in disagreement in blood sugar findings, not so much in fact as in viewpoint. He still sees only the hyperglycemia which follows a convulsion as the outstanding feature, whereas I maintain that this is merely the physiologic response to any sudden muscular activity. I find much more of significance in the peculiar low values that Stander and I and many others have seen repeatedly. It is not surprising that many eclamptic patients show high sugar values, because of the repeated muscular upheavals, but it is surprising that any

of them could be found so low as many have reported. This phenomenon, to my mind, is the one of real significance. Low levels are especially common in pre-eclampsia where the convulsion has not yet disturbed the values.

In order to explain, if possible, these peculiarly low levels seen so frequently in eclampsia, I took prolonged series of blood sugar readings at five- to ten-minute intervals in 19 eclamptics and found striking and sudden fluctuations in the blood sugar with the convulsions almost invariably preceded by a sharp fall similar to that of insulin overdosage. The actual level of the blood sugar, when this occurred, might be below, or within, or above normal values, but in relation to what it was a moment before that, or even for several readings before, it represented a sharp fall so that I coined for this the term "relative hypoglycemia." John of Cleveland has reported comparable insulin reactions and shock in diabetics with blood sugar above 200 mg., but relatively hypoglycemic when compared with the level just before the overdose of insulin was given.

I feel sure that Stander's inability to find these fluctuations and the relative hypoglycemia which precedes the convulsion with the physiologic relative hyperglycemia after them is due merely to his not having taken, in any one of his case reports which I have examined, a long enough series of readings at short enough intervals. This is particularly likely to be the answer because Laferty and his coworkers of Philadelphia as well as Siegel and Wylie of Baltimore, have repeated my studies and confirmed these findings.

After all, since these findings merely give, as yet at least, another rational basis for the use of intravenous glucose injections in preeclamptic and eclamptic patients, our partial disagreement on this does not particularly matter. Our views on treatment are the same and Dr. Stander has emphasized today, as he has before, the important relationship that should exist between the laboratory and the clinical divisions in the successful treatment of pregnancy toxemia.

DR. FRED L. ADAIR, CHICAGO, ILL.—For many years I have contended that we could not prevent or cure eclampsia by prenatal care. All we accomplish is to reduce the incidence of convulsive and comatose cases and correspondingly increase the number of preeclamptic cases.

I desire to call attention again to a group of cases which vary from the eclamptic and nephritic type. This is the hypertensive group. Essential hypertension is a vascular disorder of unknown etiology which occurs in nonpregnant women and is definitely aggravated, both temporarily and permanently, by pregnancy, and eventually results in morphologic vascular changes involving the vessels of the kidneys as well as those of other organs.

I am informed that the methods of estimating uric acid, glutathione and thioneine are not sufficiently specific and quantitatively accurate to enable one to interpret the findings in terms of disturbed metabolism and I should like to ask Dr. Stander why he associates high uric acid values with a damaged liver inasmuch as uric acid is supposed to be formed in the liver? Is the uric acid excretion increased in these cases? Is there rapid uric acid formation possibly from synthesis of fetal nucleoproteins? Is it possibly due to a starvation acidosis?

All of the chemical work done on these cases in our clinic has been carried out under the supervision of Dr. W. J. Dieckmann. The actual and relative findings are practically the same as those of Dr. Stander. It has been found that the eclamptic group shows a relatively high nonprotein nitrogen value antepartum with a rapid decrease within forty-eight hours postpartum. The values are relatively less than the normal nonprotein nitrogen ratio but show a corresponding fluctuation. This points more to a functional disturbance than to a real organic kidney lesion.

The uric acid values are also high in our series of something over fifty eclamptic and fifty preeclamptic cases. The exact significance of this is a little uncertain. It may result from alterations in diet, starvation and any functional or organic impairment.

DR. JAMES R. McCORD, ATLANTA, GA.—In 1928 in our clinic we started treating our eclamptic patients with nothing but magnesium sulphate and glucose. Our total mortality in 115 cases has been 5.2 per cent. In our last 49 cases we have lost but one woman. We have had two cesarean sections; we have done ten forceps operations and two breach extractions.

**10. A Roentgenologic Study of the Mechanism of Engagement of the Fetal Head.** Drs. William E. Caldwell, Howard C. Moloy and D. Anthony D'Esopo, New York City (Paper presented by Dr. Moloy). (See page 824, December, 1934, issue.)

#### DISCUSSION

DR. L. A. CALKINS, KANSAS CITY, Mo.—This classification of pelves may prove to be very valuable from two points of view.

In the first place, our teaching is apparently based on a large number of unrelated abstract entities, whereas we could present most of these conditions as biologic variants. Such a presentation would have the distinct advantage of relating all of these conditions one to the other and, in the case of female pelves, would merely show variation in one direction or the other from what we regard as the strictly normal. We have known for a long time that the whole pelvic girdle, and more particularly the sacrum and coccyx, is subject to a tremendous developmental variation. This variation is not only present in regard to centers of ossification but is also manifested in marked differences in rate of growth and in angulation. These variations are rarely present in the rest of the vertebral column but are really quite striking in the sacrum and coccyx.

The phylogenetic reduction of the sacrocaudal vertebrae in the high primates has long been recognized. We should, therefore, expect not only high assimilation and low assimilation pelves but also the anthropoid type, and possibly also the android type as well. One cannot help but wonder whether the proportion of android pelves will not increase in the future. I am thoroughly convinced, after a few years' trial of this teaching method, that the student will grasp the whole picture much more readily and understand the individual types of pelves much more thoroughly.

The second point of view of importance to be attached to this work is the increased ability to prognosticate the probable "parturitional" effect of the particular size and shape of the pelvis in the individual patient. Apparently the authors have been able, in the two hundred cases studied, to better foresee the probable course of labor than by previous methods. I think we shall all be very much interested in knowing whether the experience of a larger series of cases will substantiate the findings in this comparatively small group. There is some question in my mind whether the method is perhaps not too cumbersome for general use. Certainly one could not employ it as a routine in all cases and, quite as certainly, one must have a considerable experience with it before he would be able to rely upon his judgment in reading the plates.

I have real evidence that the head enters the pelvis in the transverse diameter. I cannot help but wonder, however, whether a teaching is sound when it suggests that internal pelvic measurement is no longer necessary, as the average practitioner cannot use this more cumbersome and detailed, although perhaps far superior, method of study here recommended. Moreover, the knowledge that after careful pelvic

measurements the pelvis is essentially normal allows the attendant to direct his attention to other important factors such as the resistance of the soft parts, and the effectiveness of the labor pains, either of which is more often sufficiently abnormal to produce delay and perhaps pathology than the bony pelvis.

DR. WILLIAM E. CALDWELL, NEW YORK CITY.—We have been surprised at the ease with which two films of the fetus and the pelvis can be taken between pains. When viewed with the precision stereoscope, Varney's description of the engagement of the head has been proved as the most common method in this series of cases.

Another important point which we had not recognized before is the position of the child's body to the plane of the inlet. Normally the child's body lies in the curve of the uterus at the transverse diameter, possibly slightly anterior or slightly posterior. Even before the membranes have ruptured the body is straightened out, but even in prolonged labor the axis of the uterine forces strike the plane of the inlet at an angle instead of straight up and down, as we were led to believe. In the majority of cases the contraction of the uterus in itself brings that forward since that is the point of least resistance.

I believe that this method will save a great many cesarean sections if it is done before the uterus is contracted. In five of these cases the child's head did not rotate into the anterior posterior diameter and cesarean section was done. It seems to me that Williams was right when he said, "In a difficult situation, with a good surgeon and under proper conditions, cesarean section is frequently the easiest way out, but that is not obstetrics." I believe the x-ray films will make it necessary to do fewer cesarean sections and will make labor much easier.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—This method of x-ray examination of the pelvis is extremely simple. It can be done in labor between pains, and when those films are viewed through the special stereoscope the information obtained is extraordinary. One can see if there is any disproportion, and how the head is entering the pelvis. Dr. Caldwell and Dr. Moloy have become so expert that they can prognosticate exactly how the head is going to go through the pelvis, and whether anterior or posterior rotation is going to occur. I know of nothing that has given us more satisfaction during the past year than has this method. It has probably saved many cesarean sections. On the other hand, it has enabled us to do cesarean section at the time of election where otherwise from the mere pelvic measurements one would say that certainly a trial labor was indicated.

**11. Circumcrescent and Circumvallate Placentas.** Dr. James R. Goodall, Montreal, Canada. (See page 707, November, 1934, issue.)

#### DISCUSSION

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—It is evident that in the earlier studies of the condition there has been lost the significance of the correlation between the clinical history of the pregnancy and the production of this alteration in the structure and shape of the placenta. Dr. Goodall regards the circumcrescence, either the concentric or eccentric type, as a physiologic effort on the part of the villi to preserve the life of the fetus. Holland and Ballantyne mentioned this condition as a cause of stillbirth, and yet from what Dr. Goodall has said I should think that if we made a further study of stillbirths or prematures, and this hypertrophy, we might find a considerable amount of interwoven evidence, that the clinical history of the woman and the pathology of the placenta were related in the premature birth or stillbirth of the child.

It is rather difficult for me to consider that the placenta could become as senile as Dr. Goodall considers it to be toward the end of pregnancy, beginning at the seventh month and working on. The last two months is the period for the greatest need of nutrition and support of the child, and if this compensatory hypertrophy is manifested in the villi, it would seem that the placenta should not become as aged as he seems to feel that it is at the time of birth.

I have seen three cases of erythroblastosis fetalis which Dr. Goodall mentioned. This was characterized by an intense anemia of the child at birth and the placenta was extremely pale, very light pink, and showed evidence of edema.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—Williams, in a study of 30 cases of placenta circumvallata going over his clinical histories, concluded that this abnormality was practically without clinical significance.

Dr. Hobbs of my service, with a few cases fresh in mind where there were severe clinical complications, began an investigation of our material. He pointed out that in the cases studied by Williams, the patients were near term. Hobbs divided his cases into two groups, those in which the fetuses were stillborn or died soon after birth, and those in which the babies were born alive.

In the first group the circumvallata was complete in 25, and partial in 9; in the second group it was complete in 26 and partial in 19. In the first group there were 26 stillbirths with eight other deaths where the babies had lived but a few hours. The average weight of each child was 1,000 gm. In the second group, there were 45 living children all weighing over 2,500 gm. This would seem to indicate that if the lesion developed early in the pregnancy, if it did not cause definite damage to the fetus by the time of viability, the condition is of little clinical significance, but that early in pregnancy a certain definite percentage of fetuses are lost due to the presence of this lesion.

DR. CAREY CULBERTSON, CHICAGO, ILL.—The adjustment or adaptation between the growing uterus and the growing egg has been taken for granted. I feel that this is not always the case, and therefore, after the placental plate is established, this further elaboration of the frondosum results in hypertrophy, a phase which strikes me as being very adaptable to the situation. The term "circumerescence" is one which explains that and is very well used in describing the condition.

In a series of cesarean sections we have occasionally seen a circumvallate placenta and in every case the point of imbedding was in the horn of the uterus. Theoretically the imbedding of the egg in the horn of the uterus should give us this failure of adjustment between the growing egg and the growing uterus.

DR. GOODALL (closing).—Circumerescence is not an effort on the part of the child to preserve its life. I have observed several placentas in which the whole circumference of the placenta had undergone infarction to such a degree that function was absolutely impossible in that rim and the center of the placenta had hypertrophied to a tremendous thickness, 6 cm. in some instances. Further study showed to my surprise, that the child was living on 25 per cent of its placenta. The reserve in the fetus, in the liver, in the heart, or any of the organs, is believed by physiologists to be at least 60 per cent.

As to the question of placental senility coming on before the fetus has reached its full growth, that is a problem which it is difficult to analyze. When I first put out my work on the uterine arteries, showing that degeneration in the walls of the uterus began a few days after the puerperium began, that work had not been confirmed very long before a worker wrote and said that degeneration begins before the birth of the child. A rather startling statement and yet, perfectly true since whenever the placenta has undergone infarction a triangle is formed through the

uterine wall and that wall ceases to grow. Not only is the placenta affected but the uterine wall that feeds it undergoes degeneration also.

In this work I have tried to adopt a plan which would not interfere or bring in any preconceived ideas. In the first 500 placentas that went through I purposely ignored the histories. In the second 500 I have on the sheet not only the finding of the placenta but the clinical history also. One can deduct exactly when the first sclerosis of the placenta occurred and which is the beginning of a compensatory hypertrophy.

**12. The Management of Occiput Posterior.** Dr. William C. Danforth, Evanston, Ill. (See page 756, November, 1934, issue.)

#### DISCUSSION

DR. ALFRED C. BECK, BROOKLYN, N. Y.—The author's excellent results warrant a very careful study of his routine procedures. First of all, he stresses the importance of conserving the patient's strength in the first stage. To accomplish this he recommends rest and the relief from pain. We believe that food is equally important, and we insist that our patients take ample carbohydrates, particularly in the early part of the first stage. With Dr. Danforth, we are also of the opinion that the proper management of posterior positions should begin in the first stage. We also feel that the difficulties in the second stage are proportionate to the neglect in the first stage. His high incidence of anterior rotation is in accord with our experience. Dr. Danforth attributes it to his early diagnosis. I do not think that is the whole truth. I believe that his large number of anterior rotations is due to his careful conduct of the first stage.

In the second stage an abdominal binder increases the force of the voluntary efforts, and we have found that it is very valuable in aiding rotation. Dr. Danforth awaits spontaneous rotation but he also recommends interference at the expiration of two hours. That is sound conservatism for it allows nature to do her work when she can, and when she is incompetent he recommends interference at a time when interference can be done easily, before moulding of the uterus and retraction ring dystocia increases the difficulty. His high incidence of successful manual rotations prove this point as well as his maneuver. With Dr. Danforth we also recommend the avoidance of forceps rotation because of the great injury that results from this procedure in the hands of those who are not expert. Dr. Danforth mentioned eleven failures.

DR. JOSEPH B. DELEE, CHICAGO, ILL.—I would like to recommend to the Fellows the introduction of parasacral anesthesia. Dr. Danforth mentioned that only the older anesthetics could be used to relax the cervix, but we have found that parasacral anesthesia is very practical and relaxes the lower uterine segment sufficiently so that these maneuvers can be done.

DR. EDWARD A. SCHUMANN, PHILADELPHIA, PA.—Our own conclusions and findings agree very closely with Dr. Danforth's. Ever since Pomeroy instructed us in the use of manual rotation of the occiput, I have been a devoted follower of his technic and in the years which have elapsed since that development I have tried in various ways to overcome the difficulties which sometimes occur in the manual rotation of the occiput. The chief difficulty in my hands has been the tendency of the head to slip back after manual rotation, and the necessity of keeping a hand in place when sliding the blade of the forceps in order to maintain rotation. Eventually there developed a simple manual variation of the original technic which the entire obstetric staff of the Kensington Hospital for Women have been using now for a number of years with almost uniformly good success.



The procedure consists in ignoring the head entirely, allowing it to repose in the bottom of the hand, while the finger seeks the anterior shoulder. Then with the operator's arm below the level of the delivery table a slow circular motion is carried out. Finally the head lies in the right anterior diameter, the anterior shoulder being in the anterior oblique position from which it originated. By this plan we have been able to rotate the great majority of the posterior occiputs which have resisted spontaneous rotation. When it fails, as it occasionally will with a firmly impacted head, the occiput in the hollow of the sacrum, and when we feel after due observation of the pelvis that it is probably incorrect to permit the patient to deliver as an occiput posterior, which we consider a normal delivery in certain types of contraction and do permit to take place, we rely almost entirely upon the Kielland forceps.

DR. L. A. CALKINS, KANSAS CITY, MO.—Dr. Danforth emphasized the importance of the use of the assisting abdominal hand. We have been able in a very large number of cases to rotate the head by the use of the abdominal hand alone, plus the anesthesia of course.

DR. HUGO EHRENFEST, St. Louis, Mo.—Agreeing fully with everything said by Dr. Danforth, I would like to mention two details in my technic of manual correction. The occipitoposterior head as a rule is somewhat deflected, therefore when grasped for the purpose of rotation, pressure should be exerted on forehead to favor flexion. When this is accomplished, I give two or three minims of pituitrin, simply to push the head a little deeper into the pelvis, into its corrected position.

DR. FRED L. ADAIR, CHICAGO, ILL.—It is desirable to maintain nutrition during the first stage, but one should always keep in mind the probability of having to administer a complete anesthesia. In fact, we had one fatal case from aspiration pneumonia, and we feel that the patient should have a nonresidue diet during the first stage.

The greatest difficulty with occiput posterior positions is that they never complete the first stage, and I would like to have Dr. Danforth enlighten me as to how he handles those cases. With rupture of the membranes we often get fetal distress and later maternal exhaustion and are almost forced to resort to some interference.

DR. DANFORTH, EVANSTON, ILL. (closing).—I agree to the desirability of maintaining the body fluids if the labor lasts any length of time.

I am in agreement with Dr. Calkins' idea about the assisting hand. I have felt that the abdominal hand can be used with very marked benefit in helping to get the head around.

In reply to Dr. Adair the one fetal death should be reckoned in the number of posterior cases. In this report we are considering only term labors and not prematures.

I agree with Dr. Adair that the cases which do not attain complete dilatation are difficult to deal with. I prefer to obtain as much dilatation as is possible by the forces of labor, avoiding exhaustion of the woman, and, if unavoidable, to complete the dilatation manually. This is done only when it seems essential and as infrequently as possible.

Concerning the impacted head, if the head does not enter the pelvis we do not rotate. Engagement having occurred, we do not hesitate to displace the head upward and rotate, after which forceps are applied. As it has already entered the pelvis it will, as a rule, easily come in again.

Version was done when manual rotation was impossible or had failed. In one case the procedure advocated by Dr. Piper was used, about 600 c.c. of weak soap solution being injected into the uterus prior to version.

A method of rotation by the shoulder, as suggested by Dr. Schumann, is sometimes used if rotation of the head is difficult.

**13. Hernias Into the Broad Ligament and Remarks on Other Intra-abdominal Hernias.** Drs. James C. Masson and W. Atkinson, Rochester, Minn. (See page 731, November, 1934, issue.)

#### DISCUSSION

DR. C. J. MILLER, NEW ORLEANS, LA.—Hernia into the broad ligament is unquestionably the rarest type of hernia so far reported in the abdominal cavity. Only 13 authentic cases of strangulation from defects of the broad ligament are found in the literature, and only two cases were noted in which such defects were present and unassociated with strangulation. Hunt reviewed the cases, in a recent number of *Surgery, Gynecology and Obstetrics*, and states that in cases in which pouches were the offending defect, congenital anomalies may be strongly suspected. An interesting feature of the cases was that practically all of them were in women who had borne children. The older multiparae were almost exclusively affected, but nulliparous women were not immune.

The Baldy-Webster operation may be looked upon as an etiologic factor. I am able to report one case of hernia through the broad ligament, following a Baldy-Webster operation. Three years after a suspension operation had been done, the patient complained of constant pelvic discomfort, and was not relieved by rest or other measures. An exploratory operation was done, and an opening was found from the broad ligament alongside of the round ligament. Strangulation had not occurred. It was easy to close the opening and this procedure entirely relieved her.

DR. FLOYD E. KEENE, PHILADELPHIA, PA.—One example of herniation through the opening in the broad ligament has come under my observation. This patient was admitted to the hospital with the characteristic symptoms of an acute intestinal obstruction and at operation it was found that a loop of the terminal ileum had slipped through a congenital opening in the broad ligament, situated just beneath the round ligament at the junction of its outer and middle thirds. Release of the intestine was easily accomplished by dividing the round ligament.

DR. JOSEPH B. DELEE, CHICAGO, ILL.—This condition has been found more often in multiparous women and I think it may sometimes be due to a hematoma in the broad ligament which is not observed. Also the low cervical cesarean section may, I believe rarely, lead to hernia in the broad ligament. A hernia of the broad ligament was found at a second low cervical cesarean section. I did not force the forceps through the broad ligament at her first section, since a motion picture which was made of the operation shows it was correctly performed. One should not fail to lift up the edge of the cervical wound with an Allis forceps and slip the instrument under the wound edge to avoid this error.

DR. LILIAN K. P. FARRAR, NEW YORK CITY.—The fallopian tube is enclosed in a fold of peritoneum and the two edges of the peritoneum adhere to one another below the tube. I have found it very easy to separate these edges (and push in the fimbriated end) in doing a temporary sterilization of the tube. I think it is by such a separation of the peritoneum that a hernia in the broad ligament might occur.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—I have seen two colored women with congenital fenestration of the broad ligaments, but without hernia in either case. We had one hernia through the opening caused by a Baldy-Webster operation, with no particular features of interest.

DR. MASSON (closing).—This discussion illustrates the fact that the condition of hernia into or through the broad ligament is probably more common than the literature would lead us to believe. I think that if the condition is looked for by all gynecologists and abdominal surgeons it will be more frequently observed.

Dr. Miller mentioned his case following the Baldy-Webster operation. This impresses upon us the necessity, whenever that operation is performed, of following the advice of both Baldy and Webster of stitching the edge of the ligament firmly to the broad ligament.

I would look upon hysterectomy as a radical procedure in cases where there is strangulation. The indication in such cases is to complete the operation as soon as possible. The simplest operation would be to cut down to the edge of the opening, even if it were necessary to cut through the broad ligament, the round ligament and the fallopian tube, but I would be slow to add to the difficulty by doing a hysterectomy. If there were an opening on both sides, as recorded in some of the cases, especially those following the Baldy-Webster operation, and no indication for saving the uterus, one would probably be justified in performing a hysterectomy.

There is no doubt as Dr. DeLee suggests that in low cesarean section care should be taken not to injure the broad ligament, and if it is injured it should be resutured.

Replying to Dr. Farrar, I think there were two cases in which the hernia occurred below the round ligament.

**15. The Present-Day Trend in the Treatment of Fibroids of the Uterus.** Drs. Joseph L. Baer, Ralph A. Reis, and Edwin J. DeCosta, Chicago, Ill. (See page 842, December, 1934, issue.)

#### DISCUSSION

DR. RAYMOND E. WATKINS, PORTLAND, ORE. (by invitation).—In an analysis of 100 cases of fibroids we found degeneration occurring in 48 per cent, which is higher than that of the authors' 19.4 per cent. No instance of sarcoma, however, was found in our series. Hyperplasia of the endometrium, so frequently associated with fibroids, probably also acts as an etiologic factor. In our cases we found 44 per cent of hyperplasia of the endometrium and of these 23 per cent were polypoid in character. The tendency of polypoid endometrial growths to become malignant is well recognized.

Sterility in women having fibroids is still the subject of much discussion. Our authors believe that tubal disease is of more significance than the presence of the fibroid. As far as sterility is concerned, we wish to concur in this opinion. In cases we have studied there were 16 per cent with absolute sterility, including 4 per cent single women. If the latter were deducted, this would leave but 12 per cent. However, 17 per cent of our patients had repeated abortions, being unable to carry pregnancy to term. If those of absolute sterility were added to those who were unable to go on with pregnancy, it would mean that 29 per cent were unable to reproduce. The position of the tumor in the uterus seems not to be important, the abortions occurring in the subperitoneal type as often as in the submucous fibroid. Uterine irritability undoubtedly is the important factor here.

DR. FLOYD E. KEENE, PHILADELPHIA, PA.—I shall limit my remarks to but one phase of the subject, namely the incidence of menopausal symptoms after irradiation and after hysterectomy with and without ovarian conservation.

Recently we have reviewed the results obtained in 500 cases of myoma and the incidence of menopausal reactions following various methods of treatment is summarized in Table I.

TABLE I. SUMMARY OF MENOPAUSAL SYMPTOMS

RADIUM GROUP		ROENTGEN GROUP	HYSTERECTOMY WITH OVARIAN CONSERVATION	HYSTERECTOMY WITH BILATERAL OOPHORECTOMY	HYSTERECTOMY AND OVARIAN CONSERVATION WITH CONTINUED MENSTRUATION
None	31.9%	12.5%	82.5%	20.2%	98.4%
Mild	28.8%	25.0%	11.1%	37.5%	1.6%
Moderate	22.6%	37.5%	2.5%	17.3%	0.0%
Severe	16.5%	25.0%	3.9%	25.0%	0.0%

Until a few years ago, our usual radium dosage was 1,200 mg. hours and a considerable proportion of our patients were in the late thirties and the early forties. Under these conditions, the incidence of severe menopausal reactions was over 30 per cent. More recently the dosage has been reduced to 600 mg. hours and the age limit extended to a minimum of 45 in most instances, and, as a consequence, the incidence of severe menopausal reactions has been cut in half, the effects on bleeding and tumor regression remaining about the same as with the larger dosage.

In the operative group, the value of ovarian conservation is clearly proved, since in four-fifths of the patients so treated no menopausal symptoms had developed, contrasted with one-fifth of those subjected to bilateral oophorectomy. Further the incidence of severe menopausal symptoms is six times greater in the latter group.

Approximately 20 per cent of our patients under forty-five years of age have continued to menstruate scantily after hysterectomy with conservation of one or both ovaries. In this group, more than 98 per cent have had no menopausal symptoms and in none did annoying reactions develop.

DR. BAER (closing).—The severity of the symptoms of the postradiation menopause is in direct relation to the prematurity of the induced menopause. Thirty-five years was the original arbitrary age limit under which radiation was contraindicated. General experience has raised this level to forty years. In this series 24.3 per cent of women were still menstruating at forty-six years of age. For this reason it seems desirable to consider radium, if at all, only in the fifth decade and as close to the expected menopause as can be determined.

It is further to be noted that radium is contraindicated after the menopause is established.

With regard to the failures with radium, Norris reports 8 per cent failures, Schmitz 12 per cent, Ford 21 per cent and Keene 6.5 per cent. In our series the total incidence of failures was 11.1 per cent.

Concerning ovarian conservation, the reasons for removal of one or both ovaries are not entirely dependent on the presence of pathology. There are two other reasons that have to be considered. One is mechanical. If the fibroids are so placed, conservation of the ovary becomes mechanically impossible, and it has to be sacrificed. Last, if the nutrition of an ovary is sufficiently disturbed by the removal of the fibroids, the ovary has to be removed as a prophylactic measure against cystic degeneration.

**16. The Nature of Ovary-Stimulating Hormones.** Dr. C. Frederic Fluhmann, San Francisco, Calif. (See page 668, November, 1934, issue.)

#### DISCUSSION

DR. EMIL NOVAK, BALTIMORE, MD.—With reference to the rôle of the anterior hypophysis, there are still two chief moot points. One is the relationship between the

anterior pituitary sex hormones themselves and the prolan found in the urine of pregnant women. There has been much interesting discussion, particularly in the German literature as in the long drawn out controversy between the two schools, championed on the one hand by Zondek, and on the other by Philipp. My own feeling has been that Philipp and his school have the better of this argument, and that the weight of evidence indicates that prolan is not the same as the anterior sex hormone itself, being probably of trophoblastic origin.

The other moot question is whether the follicle ripening hormone is separate and distinct from the luteinizing hormone or whether they simply represent different phases of activity of a single sex principle. Here the question is still a wide open one, with many excellent workers on both sides.

So far as the actual hormonal interchange or interplay in menstruation is concerned, the evidence is quite good on most points. I cannot criticize Dr. Fluhmann's theory because it is about the same as I have been teaching for a considerable time. There is much reason to believe, as Dr. Fluhmann has suggested, that the factor which keeps the corpus luteum active probably comes from the ovum, and that when the ovum has imbedded itself it is probably the chief source of those chemical messengers which, through the anterior pituitary, maintain the activity of the corpus luteum for such a long time after the onset of pregnancy.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—So far as I know, no human ovum has been found in the uterus at autopsy or operation when there was a definite history of the individual not missing her menstrual period. Since ovulation and impregnation, in most instances, must take place between the sixteenth and twentieth day of the cycle, the transit of the impregnated human ovum through the tube is most likely similar to that in the guinea pig.

Both gross and microscopic specimens of the premenstrual endometrium on the twenty-eighth day of the cycle, show changes which would not be compatible with the implantation of the ovum. It would, therefore, seem logical to assume that continued development of the corpus luteum and the prevention of retrograde change in the premenstrual endometrium, result from some stimulating substance given off by the impregnated ovum while it is traveling through the tube still within the zona pellucida. The stimulation may primarily affect the corpus luteum or affect it secondarily through a primary stimulation of the anterior lobe of the pituitary gland.

DR. FRED L. ADAIR, CHICAGO, ILL.—There is essential danger in the use of the anterior pituitary hormone. We had a young girl under observation who had not menstruated. Her pelvic findings were essentially negative except possibly for a little hyperplasia of the uterus. An attempt was made to use this stimulating hormone and as a result the patient developed some rather large ovarian cysts which proved to be follicle cysts. The same preparation was subsequently tried on an older woman who was scheduled for operation, in order to see whether we could repeat this performance, and it was found that she also developed a rather large follicle cyst in the ovary. Therefore, I think we should be rather cautious in the use of this as well as other hormones in women and also that we should emphasize the evidence from those two observations that there may be some definite relationship between the formation of follicle cysts in the ovary and the gonad-stimulating hormone of the anterior pituitary.

DR. JOSEPH B. DELEE, CHICAGO, ILL.—I have noticed particularly since I have been using the colposcope, that women at the menopause and after supravaginal hysterectomy may develop polypoid conditions and real polypoid masses in the stump of the cervix, and I wonder if the cervix is not under hormonal influence, just as the endometrium is.

17. **Granulosa Cell Tumors of the Ovary.** Drs. Emil Novak and James N. Brawner, Baltimore, Md. (See page 637, November, 1934, issue.)

#### DISCUSSION

DR. BENJAMIN P. WATSON, NEW YORK CITY.—Dr. Novak's emphasis on the origin of these tumors from oophoronegenic rests is particularly important as giving an explanation of the diversity of their histologic character and in their symptomatology. It is extraordinary how long the old theory of the development of the ovarian follicles from an invagination of the so-called germinal epithelium has persisted. When we picture the true development of the ovary as a differentiation of one mass of cells into ova, follicle epithelium, and stroma, it is easy to imagine how such a group of those original cells, remaining as a rest, may develop into a tumor with epithelial-like cells, or into one with resemblances to a sarcoma; and how in all of them we may find histologic changes similar to those seen in the normal ovary during its various functional activities, and how these are capable of causing similar or exaggerated functional results.

In the past two years we have had two granulosa-cell tumors pass through the laboratory of the Sloane Hospital for Women; one patient was twenty-eight years of age, nulliparous, complaining of severe menorrhagia amounting to almost continuous bleeding, unaffected by various endocrine preparations. On examination a cyst the size of an orange was discovered in the right side of the pelvis. A curettage was done and the cyst, which replaced the right ovary, was removed together with the tube. The other ovary appeared healthy. The cyst measured 8.5 cm., was yellow to greenish-gray in appearance and contained clear amber fluid. In the wall, the inner surface of which was smooth, were smaller cystic spaces. Microscopic examination of the wall showed many of the appearances described by Dr. Novak, but chiefly the macro- and microfolliculoid types. In one area there was a definite lutein-like appearance. The endometrium showed a pronounced cystic glandular hyperplasia with little gland cell activity. Since operation this patient has had three normal menstrual periods.

The other case was discovered accidentally in the routine examination of specimens. Operation was undertaken for fibromyomas with associated adnexal inflammatory disease. The woman was colored, aged fifty-five, and had had the menopause five years before. Six months prior to admission she had had some vaginal bleeding, which lasted for only one day.

There was marked thickening and adhesions of the adnexa. The right ovary was enlarged to a size of 3.5 by 2 by 1 cm. Near one pole was a small circumscribed nodule. On microscopic examination this was found to be an epithelial tumor separated from the rest of the ovarian stroma by a definite connective tissue capsule and broken up into lobules by a connective tissue framework. The epithelial cells resemble granulosa cells. Some are in solid formation, and others are arranged in a folliculoid manner. The high power view shows the superficial resemblances to primitive follicles with central ovum to which Dr. Novak has referred. Tumor cells growing in solid formation are present in the connective tissue capsule and appear to be growing within endothelial lined spaces suggestive of lymphatics.

The endometrium in this case showed no hyperplasia. It had the atrophied appearance of the endometrium of a woman five years past the menopause.

As regards the procedure, when these tumors are diagnosed I am in entire agreement with Dr. Novak that in the younger woman we are justified in being conservative as regards the uterus and the other ovary, but that in the case of those near, at, or past the menopause, complete removal of the uterus and both adnexa is the method of choice.

DR. CAREY CULBERTSON, CHICAGO, ILL.—Dr. Novak included among the granulosa-cell tumors the other tumors which are derived from the same source in the ovary, the so-called folliculomas and lutein cell tumors. He referred to the luteinization of the granulosa-cell tumors, but he did not specifically say that he included the so-called thecomas. I think this terminology, was very well made because it reduces in number the terms that are required and makes it simpler for the teacher. However, in that respect, I think there will be some continued difference of opinion on the part of the pathologists who will not yield to the idea that these tumors are all granulosa-cell tumors, merely changed because the hormone, or whatever substance it is that affects development of their cells from the undifferentiated residue of the mesenchymal nucleus, causes them to appear in these various forms. The pathologist will continue to regard the theca-cell tumor as different from the granulosa-cell tumor even if, as is true, they both affect similarly the uterine endometrium. The pathologist is apt to emphasize the differences rather than similarities. It is possible therefore to mistake the thecoma, and this tumor has been most often mistaken for sarcoma and often looks more like it than like a granulosa-cell tumor. With regard to malignancy, I am in accord with Dr. Novak's views. If these tumors take their origin in the undifferentiated residue we should expect to see the peculiarities characteristic of malignancy. But here again pathologists are none too helpful. Only recently no less an authority than McCarty has asked the question as to whether the cancer cell possesses any differentiating characteristics. Likewise research workers in embryology have suggested that growth and differentiation of early embryonic tissues are determined largely by intracellular "organizers" or chemical "energizers."

DR. FRANK W. LYNCH, SAN FRANCISCO, CALIFORNIA.—In seeking an etiology for these tumors, we are likely to revert to Waldeyer's and Pfluege's idea of the origin of the ova, theories that have been overthrown. Evans, in a publication which has not been as widely circulated as it deserves, has shown that the ova in human beings and in laboratory animals are not preformed at birth but are developed each month from germinal epithelium. So, instead of being the oldest cell in the body as we have been taught for years, we find that an ovum lasts only for a few days, probably as long as a red blood cell. Did the ova live as long as we have been led to believe they did and were always preformed at birth, inherited characteristics would be the only ones that we would be likely to develop.

These tumors are very interesting clinically in some women with unexplained hemorrhages and negative findings on examination. I have had two patients in recent years whom I had treated with radium even though I found no evident reason for the bleeding. When the bleeding returned again after several months' freedom, I removed the pelvic organs, after having carefully explored the entire abdomen. I found small granulosa cell tumors in each case: In one of them the ovary was of normal size. My entire staff now suspect the presence of this type of tumor when a woman is bleeding, and uterine cancer has been excluded by curetting, and an ovarian tumor has been ruled out by a negative pelvic examination.

The symptomatology of this tumor is very interesting. Usually, the patient with this neoplasm feels so well that she believes the bleeding is merely an indication of the return of youth. Rarely, however, the reverse holds. One of my patients with a rather large granulosa cell tumor was extremely depressed before the tumor was removed but was really rejuvenated afterward. The tumor in this case was large enough to be malignant, although the patient died a year later from an endocarditis before she had widespread metastases.

DR. NOVAK (closing).—I am familiar with the work of Evans and Swezy on the question of postnatal ova-genesis, which they think possible even in the human ovary.

While I have much respect for these investigations, I have not been convinced that their correctness has been demonstrated in the human being. While the possibility of germ cell formation even in adult life must be borne in mind, we have not seen any evidence of it as yet.

Referring to Dr. Culbertson's remarks about the thecal-cell tumors, I was impressed when the recent paper of Melnick and Kantner appeared, with the similarity of their cases with one or two of ours; moreover, the endometrial picture was exactly the same as in our granulosa-cell tumors. In many of our cases, we could see a transition from a sarcoma-like picture to the more typical epithelial picture. On the basis of the newer developments in ovarian embryology there seemed to be no justification for making a distinction between the two groups of tumors. We have, however, discussed this question more fully in the body of our paper.

Finally, it is interesting to remark, because I think it has a bearing upon the question of the etiology of vasomotor symptoms in menopausal women, that in our Case 20, the woman having already had one menopause at forty-seven, after removal of her tumor at fifty-seven went through a perfectly characteristic second menopause, with typical vasomotor symptoms. One of Schulze's patients showed the same phenomenon as did another case reported by Dworzak. This is interesting because it indicates that folliculin withdrawal is probably the initial cause of these menopausal symptoms, and makes our treatment of these with follicle hormone quite rational. At certain stages we normally get a drop in the level of follicle hormone, and it is in these cases that we get the most vasomotor symptoms. On the other hand, at certain other phases, as Zondek has shown, there is a hyperfolliculinism, and in these we are more apt to note menstrual excess. My observation has been that menopausal symptoms are usually absent or slight in menopausal women suffering with functional bleeding.

**18. The Influence of Pregnancy on Tumor Growth.** Dr. L. A. Emge, San Francisco, Calif. (By Invitation.) (See page 682, November, 1934, issue.)

#### DISCUSSION

DR. BROOKE M. ANSPACH, PHILADELPHIA, PA.—I always had been under the impression that cancer of the cervix increased with great rapidity during pregnancy. Dr. Emge's observations seem to show otherwise; five permanent cures out of six cases is very striking. This brings up the problem not only of the etiology of cancer but also of the cure of cancer. The similarity between the destructive action of a cancer cell and the destructive action of a chorion cell during nidation of the ovum is well known. Why does this destructive action cease physiologically at a certain time during placentation? Is the failure of the inhibiting influence the underlying cause of chorionepithelioma? What continues the normal into the pathologic and what is the significance of the unusual quantity of the anterior pituitary or the anterior pituitary-like hormones that appear in the blood with the development of a chorionepithelioma? These unexplained facts certainly open up many interesting fields of conjecture.

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—It is sometimes a thankless job to tear the curtain from popular fallacies as Dr. Emge has done. His experiments have shown just about what we might expect. Clinically, observations may have led us astray, and yet they have been quite justified in the limited light of existing knowledge. When we see a uterus in a patient less than three months pregnant, with a tremendous myoma, we might be excused for concluding that the myoma grew unusually rapid, and yet Dr. Emge's experiments have shown that this tumor growth



is *pari passu* with the uterus, due undoubtedly to the fact that myomas being constructed of the same tissue as the uterus, respond to the same hormonal stimulation.

Dr. Emge confirmed in his experimental work the fact that ovarian tissue tumors do not usually grow. These are usually small cysts but even good-sized ones may be hidden behind the uterus and discovered only after delivery.

His experiments show, as clinical experience would anticipate, that only those tumors increase which are capable of hormonal stimulation.

DR. EMGE (closing).—In regard to cancer of the cervix in pregnancy, I still believe that the degree of curability is largely dependent upon whether or not this tumor is discovered early. The mere fact that fibroids are more readily discernible during pregnancy does not necessarily indicate that they grow. It was demonstrated by Borner that many of these tumors migrate toward the surface during the progressive enlargement of the uterus, which makes them more readily available to the tactile sense. The enlargement of pure leiomyomas may be considered an actual growth response, since involution is less marked than in fibromyomas or fibromas. I have studied some 40 fibromyomas removed during pregnancy and have invariably found that active cellular hypertrophy comes to a standstill somewhere near the sixth month. In most of these tumors the apparent enlargement of cells, particularly muscle cells, could be easily explained on the basis of a marked increase in intracellular fluids. In only a few of these tumors could we demonstrate sufficient hypertrophy to allow us to believe that the tumor had actually grown. We have not been able to demonstrate to our satisfaction that hyperplasia is an important factor in the enlargement of fibroids during pregnancy.

**19. Demonstration of the Lymphatic Circulation in the Pelvis of the Living Woman by the Roentgen Rays.** Dr. George Gellhorn, St. Louis, Mo. (See page 769, November, 1934, issue.)

**20. The Innocuousness of Rupture of the Membranes Early in Normal Labor.** Dr. Edward L. King, New Orleans, La. (See page 763, November, 1934, issue.)

#### DISCUSSION

DR. JOSEPH B. DELEE, CHICAGO, ILL.—I believe that the principle that the bag of waters is a protective mechanism for the cervix still holds. If one knows the physics of the uterine action he will easily see the dilating effect of the bag of waters on the cervix; if one denies the bag will dilate the cervix, he must admit the head also will not do so after the membranes are ruptured. Rupture of the membranes is dangerous. In transverse presentation the dilatation is almost completed without the bag of waters but it is not the complete dilatation as you get it with the normal mechanism. Now when the cervix dilates the longitudinal fibers pull up all the tissue, but the mucous membrane may follow too slowly and if the membranes are ruptured the endocervical mucosa is forced down by the head like a glacier slide and produces a condition like an everted anus. Injury of the cervix is one of the causes of the numerous cervical infections.

As to the baby's brain, there are silent areas in the brain which do not reveal their injuries when the baby is young. When the bag of waters is intact the baby's brain is protected and after it is ruptured the brain gets the full force of the action of the uterus. That has been proved in a rather crude way by experiments on guinea pigs, in which the brain was trephined with resulting increased blood pressure, hyperemia, etc.

DR. H. J. STANDER, NEW YORK CITY.—From our experiences at the Lying-In Hospital I agree with the conclusions of Dr. King. It seems fairly well established

that the bag of waters does not play as important a rôle in the dilatation of the cervix as we have heretofore believed. The work of Guttmacher and Douglas, as well as that of Quigley, showed fairly conclusively that labor is not lengthened by early rupture of the membranes.

I have reviewed 4,250 consecutive full-term and premature deliveries. Of this group 2,047, or 48 per cent, had ruptured membranes, either spontaneously or artificially, prior to the second stage, which means either before labor started or during the first stage of labor. In Table I is shown the time of rupture of the membrane in these 2,047 patients. In only two cases did we induce labor by rupture of the membranes; and in only 7.06 per cent of the cases were the membranes ruptured artificially, for some reason or other, prior to the second stage.

Table II shows that in 92 per cent or more of these cases, the presentation was vertex. The incidence of puerperal infection, as shown in Table III, is about 10 per cent in the patients in whom the membranes ruptured spontaneously prior to the

TABLE I. TABLE SHOWING TIME OF RUPTURE OF MEMBRANES

	PREMATURE DELIVERY	FULL-TERM DELIVERY		TOTAL	% OF 2,047
		OPERA- TIVE	SPON- TANEOUS		
Labor induced by rupture of membranes, artificially	0	1	1	2	0.097
Membranes ruptured spontaneously before onset of labor	34	183	522	739	36.10
Membranes ruptured in 1st stage of labor	33	323	950	1306	63.80
Spontaneously	24	254	872	1150	56.2
Artificially	9	69	78	156	7.6

TABLE II. NUMBER OF CASES WITH VERTEX PRESENTATION

	PREMA- TURE DELIVERY	FULL-TERM DELIVERY		TOTAL	GRAND TOTAL	% GRAND TOTAL
		OPERA- TIVE	SPON- TANEOUS			
Labor induced by artificial rupture of membranes		1	1	2	2	100
Membranes ruptured spontaneously before onset of labor	28	144	510	682	739	92.28
Membranes ruptured in 1st stage of labor	24	256	931	1211	1306	92.72
Spontaneously	18	192	855	1065	1150	92.60
Artificially	6	64	76	146	156	93.58

TABLE III. NUMBER OF CASES OF PUERPERAL INFECTION\*

	PREMA- TURE DELIVERY	FULL-TERM DELIVERY		TOTAL	GRAND TOTAL	% GRAND TOTAL
		OPERA- TIVE	SPON- TANEOUS			
Labor induced by artificial rupture of membranes		0	0	0	2	0
Membranes ruptured spontaneously before onset of labor	5	35	31	71	739	9.60
Membranes ruptured in 1st stage of labor	2	71	74	147	1306	11.25
Spontaneously	1	57	61	119	1150	10.34
Artificially	1	14	13	28	156	17.94

\*In 2,620 full-term + premature deliveries in 1933 there were 228 cases of puerperal infection. Incidence = 8.702 per cent.

onset of labor, as well as in those cases in whom the membranes were ruptured in the first stage of labor. This is approximately the incidence of puerperal infection for the whole clinic, the figure being 8.7 per cent. When, however, we consider the patients in whom the membranes were ruptured artificially, the incidence of puerperal infection is definitely elevated, being 17.9 per cent. In 26.9 per cent of these patients labor was definitely prolonged to thirty hours or more. This undoubtedly is one factor in the increased incidence of infection. Although in the present study all other factors have not been evaluated, and we are unable to definitely ascribe the higher morbidity to the artificial rupture of the membranes, we feel that this increased incidence of puerperal infection in the patients with artificially ruptured membranes must be taken as a note of warning and that the rupture of the membranes, as a means of inducing labor, must not be regarded too lightly with respect to infection.

Table IV shows the incidence of infantile mortality, in the various groups of patients in whom labor was induced artificially, by rupture of the membranes, as

TABLE IV. INFANTILE MORTALITY\*

	PREMA- TURE DELIVERY	FULL-TERM DELIVERY		TOTAL	GRAND TOTAL	% GRAND TOTAL
		OPERA- TIVE	SPON- TANEOUS			
Labor induced by artificial rupture of membranes		0	0	0	2	0
Membranes ruptured spontaneously before onset of labor	10	18	11	39	739	5.27
Membranes ruptured in 1st stage of labor	12	40	16	68	1306	5.21
Spontaneously	6	27	13	46	1150	3.10
Artificially	6	13	3	22	156	14.10

\*In 2,651 full-term + premature infants in 1933 there were 121 infantile deaths. Incidence = 4.565 per cent.

well as in those in whom the membranes ruptured, either spontaneously or artificially, during the first stage. Here again it will be noted that there is a marked difference between the patients with spontaneous rupture of the membranes and those with artificially ruptured membranes. The fetal mortality in the later group is 14.1 per cent, as compared with the clinic incidence of 4.5 per cent.

From this short study I am led to believe with Dr. King that the less we interfere with the normal progress of labor, so long as it is normal, the better will be our results. We do not hesitate to employ rupture of the membranes for the induction of labor where we feel that it is indicated, but we are convinced that it is not the procedure of choice in all patients where labor should be initiated.

Two factors are of extreme importance in determining the latent period and the success of this method of induction of labor; these are the length and the dilatation of the cervix. The latent period, as Gutmacher and Douglas showed, is lengthened nearly four times in patients with long cervices, compared to those with shorter cervices. The length of the cervix could also be directly correlated to the duration of the labor, the longer the cervix the longer the labor. Furthermore, dilatation of the cervix affects the latent period, patients with closed cervices having a long latent period, and patients with patent cervices having shorter latent periods. However, the dilatation of the cervix at the time of the rupture of the membrane does not materially affect the duration of labor.

From this we must conclude that rupture of the membranes, before labor or early in labor, either artificially or spontaneously, in a patient with a long, closed cervix carries with it two possibilities, a long latent period and a long labor, both of which must necessarily be associated with increased complications to mother and child. It

must, therefore, be clear to all that rupture of the membranes as a means of induction must be carried out in carefully selected and studied patients, and is not a method that can be applied to all patients without serious consequences.

DR. WILLIAM E. CALDWELL, NEW YORK CITY.—The x-rays have shown that the normal position of the babies is transverse and the function of the rotation is not only to straighten the child's body but to bring it forward toward the front of the uterus. The early rupture of the membranes apparently allows this process to be established much more quickly than if the membranes are intact. We all feel safe, as far as the baby is concerned, when the membranes are intact.

DR. JOSEPH L. BAER, CHICAGO, ILL.—I have the definite feeling that if Dr. King wants an endorsement from the American Gynecological Society of the relative safety of artificial rupture of the membranes in ordinary uncomplicated labor, that endorsement should be withheld. I cannot help but feel that the innocuousness of artificial rather than spontaneous rupture depends on the character of the cervix and the entire labor picture; in other words, it is a situation which demands clinical judgment. We all rupture the membranes under certain conditions, but to proclaim it as a legitimate procedure merely with the thought that it will expedite labor, will lead the profession at large into many unhappy predicaments.

DR. KING (closing).—I do not wish to be misunderstood as advocating the indiscriminate rupture of membranes early in labor merely for the purpose of expediting labor, nor do I feel that the rupture is at all times innocuous nor that the protection to the fetal head can by any means be disregarded. Fitzgibbon said that he is fully convinced that the bag of waters does not play any part in the dilatation of the cervix. That, I think, is not correct and desire to emphasize my conclusions.

I do not want to leave the impression that an early case of rupture of the membranes is entirely innocuous, but that in early cases we should hunt for dystocia or difficulties that may be encountered and be prepared for them. If we cannot find abnormalities we can feel reasonably comfortable and should not be forced or hastened into unwise and unnecessary procedures. The induction of labor by artificial rupture of the membranes is still in the experimental stage. It seems to have brought good results but I think we must watch very carefully the use of pituitrin in combination with this procedure.

**21. Total Abdominal Hysterectomy: Anatomy and Technic.** Dr. Lillian K. P. Farrar, New York City. (Original paper appears in the current volume of the Society's Transactions.)

**22. A Report of 565 Vaginal Hysterectomies Performed for Benign Pelvic Disease.** Dr. N. Sproat Heaney, Chicago, Ill. (See page 751, November, 1934, issue.)

#### DISCUSSION

DR. HAROLD O. JONES, CHICAGO, ILL.—We believe that the average mortality and morbidity in complete hysterectomy is considerably higher than that given in this report today. Figures thus obtained are not from parallel cases. The mortality figures are not so much influenced by the removal of the cervix, but by the natural increased risk from time-consuming traumatic dissection of adnexal pathology.

In an unreported series of 100 cases operated by a member of this Society where the pathologic conditions were exactly parallel, the mortality and morbidity in complete removal was more than two times that in the supracervical operation.

In our clinic we have never been able to demonstrate that any infection has come from a supravaginal amputation of the cervix. We are further convinced that evi-

dence has not yet been produced to necessitate the removal of the cervix after removal of the uterus on account of any increased incidence of carcinoma of the cervix. It has not yet been established that cervical lacerations and infections are definitely connected as an etiologic factor in carcinoma. We believe that the discharges and various conditions of the cervix can be controlled much more simply by subsequent cautery.

With regard to Dr. Heaney's paper, we very strongly subscribe to the vaginal method of removing pelvic tumors, but have restricted our procedures to those that are easily accessible, freely movable, and those that are present in women who have some relaxation. We have not yet had the temerity to attack the larger tumors in nulliparous women. In women with considerable relaxation we prefer the vaginal route.

Our technic differs somewhat from that illustrated in Dr. Heaney's picture in that we dissect considerably more in trying to correct the relaxations. Two years ago we reported 2,500 plastic operations, including 168 complete vaginal hysterectomies, done over a period of ten years and in those ten years we had a mortality of three, which again emphasizes the point that Dr. Heaney made of the marked reduction in mortality and morbidity in cases operated upon by the vaginal route.

DR. EDWARD H. RICHARDSON, BALTIMORE, MD.—Dr. Farrar has built up a strong argument, to be sure, in favor of complete as compared with subtotal hysterectomy. Nevertheless and in spite of the fact that I too sponsor an operative technic for complete hysterectomy, I cannot help but feel that, except in the larger clinics and in the hands of experienced gynecologists, there will undoubtedly be both a higher mortality and a greater morbidity following the complete operation than would be the case in the incomplete one. I think this is also true with reference to vaginal hysterectomy in the more difficult types of cases. I do not routinely remove the cervix. I do so only when I can be satisfied that there is some demonstrable pathology that will predispose to the development of carcinoma, or where there are cystic glands with the possibility of focal infection. I think in that group of cases the cervix should be removed, but where there is a perfectly normal cervix I cannot yet bring myself to believe that the operative procedure is as simple and as safe as subtotal hysterectomy.

I am not yet prepared to report on a sufficient number of my own panhysterectomies. I have not yet reached my first one hundred cases but have had no mortality and no serious morbidity.

I am sure all of us are impressed with this series of cases of Dr. Heaney's in which he has had almost no mortality. Therefore, one may now safely choose between complete hysterectomy by the vaginal route or by the abdominal route and have available any one of a half dozen or more procedures from which he may suit his individual taste.

DR. GEORGE GRAY WARD, NEW YORK CITY.—I believe that there is great danger in cutting across the cervix. I will illustrate this by reciting one case I had some years ago at the Postgraduate Hospital. The patient had a fibroma. The routine supravaginal hysterectomy was done and the patient died within thirty-six hours of a virulent streptococcal infection. We were fortunate in getting an autopsy and as we got a pure streptococcus from the abdominal cavity, the uterus, which had not been disturbed, was opened and a pure streptococcus was obtained from the endometrium. Infection is often present there, and I cannot see how there would not be some danger in cutting across the cervix. In our service at the Women's Hospital in some 650 cases of cancer of the cervix we ran across 47 that had been subjected to a supravaginal hysterectomy, or 7 per cent. If those cases had had the cervix removed at operation, they would not have developed cancer of the cervix subsequently.

Another point is that I believe when it is necessary to irradiate a stump left after hysterectomy that we have a very definitely increased danger of injury to the bladder. With this conviction, having studied our complications quite carefully, when it is necessary to treat the stump I have reduced the initial dosage and repeat as necessary for fear of having an untoward result, by causing a fistula or even an intestinal injury. We had one case that came to autopsy with intestinal fistula and which showed the loop of intestine adherent to the cervical stump which had been irradiated. Therefore, given a case where we can without danger to the patient remove the whole uterus, it seems to me the wise thing to do. I, of course, recognize the point just made that there may be complications such as Dr. Jones spoke of. Very often the danger is materially increased in attempting to do a panhysterectomy. Where the cervix is normal, and the conditions difficult, my judgment would be to do a supravaginal hysterectomy, but where panhysterectomy can be done safely it is the desirable procedure.

DR. GEORGE GELLHORN, St. Louis, Mo.—What commonly goes under the name of abdominal hysterectomy is a misnomer. Hysterectomy means extirpation of the entire uterus, but what is being done in most instances, is only an amputation of the uterus. It is a sad reflection that many men who attempt pelvic operations are not sufficiently familiar with the technic of hysterectomy. The result is that all patients are subjected to one and the same type of operation, even if the condition of the cervix or other specific features of the case obviously call for a total removal of the uterus. I have in mind at this moment the case of a young woman of twenty-three who underwent a supravaginal amputation; the surgeon then put her in lithotomy position and sewed up a deep tear in the cervix. A year later she came into our clinic with a carcinoma of the cervix. That brings me to the problem of stump carcinoma. Dr. Farrar had 47 cases in her series. Only last month I reported 44 stump cancers. I maintain that we have at present no method of prevention of uterine cancer that is absolutely certain except the *total* removal of the uterus in all cases where we have to perform hysterectomy. That is the only known method of prevention of cancer; and it is the strongest argument in the controversy of total *versus* subtotal hysterectomy.

DR. WILLIAM P. HEALY, New York City.—I believe that we must not be too much influenced by what has been said about stump cancer since we must know in each case how early the symptomatology of the cancer appeared following the supra-cervical hysterectomy because the patient may have had cancer at the time of her hysterectomy. Although it is difficult to get correct figures on stump cancer following hysterectomies, we are unable to determine that more than four-tenths of 1 per cent are apt to develop cancer subsequently in the cervix.

Recently Dr. A. N. Arneson reviewed 2,600 cases of cervical cancer at the Memorial Hospital. There were but 67 cases in that series that could be regarded as legitimate cases of cancer developing in the cervical stump after a preceding supravaginal hysterectomy. He took as an arbitrary line of division the fact that the symptoms must not have appeared sooner than three years following the hysterectomy. I think that decision is reasonable because we know that cancer may remain latent in the cervix for a period of time before it becomes recognized. Taking that as his line of starting, only 67 out of 2,600 cases could be found or 2.6 per cent.

DR. FARRAR (closing).—The criticism has been made that total hysterectomy is time-consuming. When one is doing total hysterectomy routinely, it requires only a few minutes more to remove the cervix.

Dr. Ward spoke of infection in supravaginal hysterectomy. A culture made from the cavity of the uterus removed because of submucous fibroids or cancer in the fundus shows not infrequently a positive growth.

Irradiation for cancer of the cervix seems to have reached its peak. We know that despite heavy doses of radium that cancer often recurs, not only by metastases, but locally in the pelvis, and that high voltage x-ray of the pelvis does not destroy the carcinomatous glands and by stimulating connective tissue it does constrict the ureters. Renal insufficiency and death may follow from this compression.

It is of statistical interest only to know whether cancer in the cervix was recognized before or after a given date following a supravaginal hysterectomy. We know that prophylaxis is the best hope we have to lessen cancer and if a total hysterectomy be performed then an unrecognized cancer in the cervix would not be left nor could the patient develop cervical cancer later.

DR. HEANEY (closing).—I want to draw your attention again to the fact that in this series of cases there were four unsuspected carcinomas of the cervix, four carcinomas of the corpus uteri and three carcinomas of cervical polyps. When you do not suspect a carcinoma in a case you are operating upon vaginally and the whole operation is concluded without suspecting that a carcinoma is present, you may be sure that carcinomas will be overlooked much more often by the abdominal route, and particularly if operating supravaginally. There has never been any proof which I thought sufficient that lacerations of the cervix are productive of cancer of the cervix, and though removing the obviously diseased cervix will make the patient much more comfortable by relieving her of leucorrhea, yet if you leave the apparently normal cervix there is no evidence that you will lessen carcinoma of the stump subsequently.

Since I limited this paper to those cases which were benign and did not include the cases that were cancerous, I might say that there were 18 cancers of the body of the uterus without a death, and 25 cases of cancer of the cervix with two deaths. These cases were treated with an entirely different technic and hence were not included in this report.

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## Item

### American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants for certification will be held in various cities of the United States and Canada on Saturday, March 24, 1935. Case histories for review may be filed with the Secretary any time prior to this date after the approval of a candidate's credentials.

The general examination for all candidates will be held in the Atlantic City General Hospital on Monday, June 10 and Tuesday, June 11, 1935, immediately prior to the scientific session of the American Medical Association.

An unusual number of candidates is expected for this meeting, and on this account early application is advisable in order to qualify. Applications for Group B candidates must be received not later than February 23, 1935, and for Group A candidates not later than May 10, 1935.

For further information, booklets, and application blanks apply to the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, (6) Pa.

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## Errata

In the Caldwell article in the December issue of the Journal, page 838, Fig. 11 should be Fig. 9 and Fig. 9 should be Fig. 11.

In the same article on page 836 the following credit should appear under Fig. 8: From William's *Obstetrics* published by D. Appleton-Century Company.

## Books Received

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THE STORY OF CHILDBIRTH. By Dr. Palmer Findley. With many illustrations. Doubleday, Doran and Co., Inc., Garden City, 1933.

THE STORK JOINS THE BLUE EAGLE. By Fred'k M. Margaretten, M.D. Illustrations by George S. Jacobs. Wamba Printery, Brooklyn, 1934.

AIDS TO OBSTETRICS. By Leslie Williams, Obstetric Surgeon to Out-patients, St. Mary Hospital, etc., London, tenth edition, William Wood & Co., Baltimore, 1934.

HEALTHY BABIES AND HAPPY BABIES. By Josephine Hemenway Kenyon, M.D. Little, Brown, and Company, Boston, 1934.

THE PROSPECTIVE MOTHER. A Handbook for Women During Pregnancy. By J. Morris Slemmons, M.D. Third edition, D. Appleton-Century Co., Inc., New York, 1934.

OPUSCULA SELECTA NEERLANDICORUM DE ARTE MEDICA. Varii auctores de symphysiotomia. Aangeboden door het Nederlandsch Tijdschrift voor Geneeskunde, 1934.

MATERNAL MORTALITY IN PHILADELPHIA, 1931 to 1933. Report of committee on maternal welfare, Philip F. Williams, M.D., chairman, Philadelphia County Medical Society, 1934.

THERAPIE DER FRAUENKRANKHEITEN. Von Professor Dr. W. Benthin, Koenigsberg i.P. Mit 23 Abbildungen im Texte. Verlag von Urban & Schwarzenberg, Berlin and Wien, 1934.

HORMONE UND SEKRETION. Von Dr. Fritz Laquer, Professor an der Universitaet Frankfurt. Zweite, verbesserte und bedeutend erweiterte Auflage. Verlag von Theodor Steinkopff, Dresden, 1934.

THE CHEMISTRY OF THE HORMONES. By Benjamin Harrow, Ph.D., Associate Professor of Chemistry, City College of New York, and Carl P. Sherwin, M.D., of St. Vincent's and French Hospital. Williams and Wilkins Company, Baltimore, 1934.

DYNAMICS OF POPULATION. By Frank Lorimer and Frederick Asborn. The Macmillan Company, New York, 1934.

TUMORS OF THE FEMALE PELVIC ORGANS. By Joe Vincent Meigs, Instructor in Surgery, Harvard Medical School, etc. With 261 illustrations. The Macmillan Company, New York, 1934.

SYNOPSIS OF PEDIATRICS. By Dr. John Zahorsky, Professor of Pediatrics, St. Louis University Medical School, etc. With 77 illustrations in the text and 6 color plates. The C. V. Mosby Co., St. Louis, 1934.

SYNOPSIS OF GENITOURINARY DISEASES. By Austin I. Dodson, Professor of Genitourinary Surgery, Medical College of Virginia, etc. With 111 illustrations. The C. V. Mosby Co., St. Louis, 1934.

STOEKEL'S HANDBUCH DER GYNAEKOLOGIE. Sechster Band, zweite Haelfte: Die Klinik der Uterus Tumoren bearbeitet von Esch, Martius, Pankow, Peham und Schoenholz. Mit 160 zum Teil farbigen Abbildungen im Text. Verlag von J. F. Bergmann, Muenchen, 1934.

CONCEPTION PERIOD OF WOMEN. By Dr. Kyusaku Ogino. Medical Arts Publishing Co., Harrisburg, Pa.



# Correspondence

## Pupillary Reactions in the Friedman Test\*

To the Editor:

IN THE February, 1934, issue of this JOURNAL, Davis, Konikov and Walker describe a new method for reading the Friedman modification of the Aschheim-Zondek test. They observed the immediate eye reaction of the test animal following intravenous injection of urine. The criterion for a positive diagnosis was contraction of the pupils. Later, they also included dilatation of the pupils as an index of a positive reaction. They reported 87 per cent correct diagnoses in 154 positive tests and 80 per cent correct diagnoses in 97 negative tests.

In view of the simplicity of the method, we have attempted to confirm their findings. We have applied this method of reading to 100 clinical and 23 experimental tests. Our routine technic includes two intravenous injections of 7.5 c.c. of urine at twenty-four hour intervals with laparotomy forty-eight hours after the primary injection. Observations were made on 100 consecutive primary injections and 66 secondary injections. The experimental tests were made with fractional amounts of urine varying from  $\frac{1}{2}$  c.c. to  $\frac{1}{80}$  c.c.

The data obtained in reading the pupillary reactions are presented herewith:

100 primary injections	7.5 c.c. urine	50.0% correct
66 secondary injections	7.5 c.c. urine	42.1% correct
23 fractional injections	$\frac{1}{2}$ c.c.— $\frac{1}{80}$ c.c.	69.0% correct
189 injections		53.4% correct

Of 66 cases having two injections:

Readings agreed after primary and secondary injections 44

Readings disagreed after primary and secondary injections 22

Of 100 clinical tests: Friedman—pos. 52; Neg. 45; quest. 3

Eye react. pos. 60; neg. 40.

All eye readings were made under uniform lighting conditions. Of the 117 positive diagnoses made by observations on the eyes, contraction of the pupils were noted in all but 5, these latter showed dilatation. Each reading was checked by two observers.

Several interesting facts were noted. Most of the test animals, on being transferred from the cages to the injecting table showed definite dilatation of the pupils. As the animals rested, the pupils contracted. If the animal became at all excited, there was a very definite dilatation of the pupils, hence, if the rabbit jumped during the injection, it was most difficult to make a true reading of the pupils. Naturally, it was much easier to observe the pupils in white rabbits than in the darker strains.

Following the method of reading the Friedman test by observing the immediate effect on the pupil as outlined by Davis, Konikov, and Walker, we obtained correct readings in 53.4 per cent of 189 observations.

I do not believe that this method offers a reliable means of reading the Friedman test.

F. J. SCHOENECK, M.D.

103 MEDICAL ARTS BUILDING,  
SYRACUSE, N. Y.

\*Aided by a grant from the Hendricks Research Fund.

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## Original Communications

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### A NEW ACTIVE PRINCIPLE IN ERGOT AND ITS EFFECTS ON UTERINE MOTILITY\*

#### A PRELIMINARY REPORT

M. EDWARD DAVIS, M.D., FRED L. ADAIR, M.D., GERALD ROGERS, M.D.,  
M. S. KHARASCH, PH.D., AND ROMEO R. LEGAULT, PH.D., CHICAGO, ILL.  
(*From the Department of Obstetrics and Gynecology, and the Department of Chemistry, The University of Chicago*)

ERGOT is a fungus which attacks rye, and less frequently wheat, barley, and oats. Although it has become of major importance in obstetrics, its early history is intimately associated with the history of civilization. The fungus infected large areas of rye and other grains in various parts of Europe, making them unfit for human consumption. The widespread use of these infected grains led to epidemics of ergotism among the people. Thus, ergotism, or "St. Anthony's Fire," became the scourge of civilization and carried in its wake suffering, deformity, and death.

European midwives knew of the medicinal effects of ergot as early as the eighteenth century. It remained, however, for John Stearns of Saratoga, New York, first to describe the use of ergot to the medical profession in 1807. Many interesting accounts of this original contribution exist. Its therapeutic effect was so marked and the indications for its use so broad that it soon enjoyed widespread popularity. Ergot soon became one of the most useful as well as one of the most dangerous therapeutic agents.

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\*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

Stearns originally administered ergot in the form of a decoction or powder. His technic was to boil one-half dram of powdered ergot in one-half pint of water, and to give one-third of this fluid to the patient every twenty minutes until the pains began and became strong. The powder was recommended in 5 to 10 gr. doses. He and other early observers noted that following the administration of this crude ergot, labor progressed rapidly and often terminated suddenly. He stated in one of his contributions that a patient in labor rarely detained him more than three hours following the use of this drug. Furthermore, the administration of the drug frequently produced violent gastrointestinal disturbances and vomiting.

Later, clinicians noted the ill-effects of the indiscriminate use of ergot in labor. Conservative physicians advised against its administration during the first and second stages of labor, and suggested that it be limited to the postpartum period where atony and hemorrhage necessitated oxytocic drugs.

The crude decoction of ergot made by Stearns at the bedside was not suitable for accurate therapeutic administration (1) because the amount of its active ingredients varied and no accurate dose could be administered; (2) the odor and taste were disagreeable, often upsetting the patient; and (3) the preparations were frequently completely inactive. However, in the light of our present work Stearns' crude preparation probably contained the new active principle which we are about to describe.

#### ALKALOIDAL NATURE OF ERGOT

It may be of interest to digress for a moment to define the term "alkaloid." The word is used, in general, rather loosely. It implies a nitrogenous substance. Some chemists hold that it is the substance which may be precipitated in a very dilute solution by a number of chemical reagents, such as Mayer's reagent (solution of potassium mercuric iodide) or sodium sulphate, etc. Mayer's reagent is perhaps the most sensitive. It will give an opalescence and finally precipitate some of the ergot alkaloid in a dilution of one part in two million.

Because of the many ingredients in ergot it has been designated a veritable treasure house of pharmacologic constituents. Biologically, the amines and alkaloids have been considered the most active; therefore, they have been studied extensively. The amines, histamine and tyramine, occur in such small quantities in ergot that they probably exert no oxytocic activity. When given in amounts many times that found in ergot, they have proved inert. Moir, and Adair and Davis have shown that a 2 mg. dose of histamine, which is large enough to cause a general reaction, is ineffective on the human uterus.

Since the work of Tanret in 1875, who isolated ergotinine, six distinct compounds of a so-called alkaloidal nature derived from ergot have been described. Ergotoxin

(hydro-ergotinine) was discovered by Barger and Carr in 1906. Further work proved that these two substances were related and that only ergotoxin was biologically active. Two other alkaloids were isolated from ergot by Stoll in 1918, namely, ergotamine and ergotaminine. Again, one of these, ergotaminine, has been considered biologically inactive. More recently, a fifth alkaloid, sensibamine, has been isolated from ergot, and is sold in this country under the trade name of "Ergone." The desirable oxytocic activity in ergot has been ascribed to these alkaloids. This idea is so firmly established that the alkaloidal content of a preparation of ergot has been used as the index of its therapeutic effect.

#### METHODS OF STANDARDIZATION

The various methods of biologic assay depend on the alkaloidal content of the drug. Barger states in his monograph on *Ergot and Ergotism*, that the quantity of total alkaloids is a measure of its physiologic activity. There are three methods of assay of ergot for potency in common use today. The cockscorn method has been given official recognition in the United States Pharmacopoeia. This method makes use of the phenomenon of ergotism. A standard fluid extract of ergot when injected into the breast muscle of a cock, in a dose not exceeding 0.5 c.c. per kilogram of body weight, i.e., about 1 c.c. per fowl, will show marked bluing of the cockscorn. These fowl are all standardized. The Broom-Clark method of biologic assay has become official in the British Pharmacopoeia. Here the pharmacologic antagonism of ergot and epinephrine is utilized. When isolated uterine strips from guinea pigs or rabbits are treated with epinephrine, the motor action of this drug is abolished by a standard ergot preparation.

M. I. Smith of the United States Public Health Service uses a chemical method of assay, based on the fact that the alkaloids, after extraction from the fluid ergot extracts, may be estimated colorimetrically in a more or less crude condition by means of the very delicate reaction with para-dimethylaminobenzaldehyde. Of thirty-eight fluid extracts thus assayed, 26 agreed within 15 per cent with the Broom-Clark method. (The agreement with the cockscorn method was less satisfactory.)

#### PREPARATIONS IN USE

The alcoholic fluid extract of ergot is the official preparation in the pharmacopoeias of most countries. The alcoholic content is variable, although it has been gradually increased so that now 49 per cent is used in the U.S.P. preparation. The most conservative preparation is the B.P. aqueous extract in which water is used in the extraction of the crude drug, to which alcohol is then added as a preservative.

Since its introduction, ergotamine (Stoll) in its pure form became exceedingly popular in ergot therapy. It was thought, theoretically, that if all the desirable physiologic activity resided in the alkaloidal

content of the crude drug, the pure alkaloid should prove ideal. An extensive literature has accumulated since the introduction of this drug. Recently, sensibamine and ergoclavine, the new members of this family of alkaloids, have been introduced into therapeutics:

Moir, in 1932, while studying the B.P. aqueous extract of ergot, noted that although it was low in alkaloidal content it proved to be high in physiologic activity when tested on the human uterus. Thus, for the first time it was suggested that all the oxytocic activity present in ergot might not reside in its alkaloids. Since we had been working on the same subject, independently, Moir's publication again focused our attention on the ergot problem.

#### METHOD OF STUDY

We have described a method of study of the physiologic activity of the human uterus in a previous communication. It occurred to us that this method which was first described by Bourne and Burn, offered possibilities for a review of the pharmacologic actions of the common oxytocic drugs used in obstetrics. Although our first report concerned itself chiefly with the physiology of normal uterine motility, we likewise studied the action of pituitrin and its fractions and some of the other common oxytocics including ergot preparations. This work on ergot has been continued and expanded in collaboration with Kharasch and Legault of the Department of Chemistry of the University of Chicago.

Our first problem concerned itself with the stabilization of the fluid extract of ergot. Innumerable attempts have been made to stabilize this preparation, but one may say truthfully that as yet no one has found a satisfactory method of preventing its deterioration. Smith and Stohlman found that elevated temperatures or the addition of oxidizing agents hastened the deterioration of the physiologically active alkaloids, while low temperatures and the addition of reducing substances retarded it, but that the control of the pH was of doubtful value. They recommended that the fluid extract of ergot could best be preserved by the addition of a reducing agent. It was also suggested that the material be distributed in small vials so as to avoid oxidation when exposed in large bottles. However, these suggestions did not solve the problem of providing an ergot preparation which was stable and certain in its oxytocic activity. We were convinced after a few experiments that the stabilization of such a complicated mixture as the fluid extract of ergot was not an easy task. Furthermore, the oral administration of the fluid extract has other serious objections in that its taste is bad, it is irritating, and gastrointestinal disturbances are common following its use. At

times it causes violent nausea and vomiting. It was, therefore, decided to investigate the problem in greater detail, so we began with the study of the crude drug itself.

The apparatus used for the study of human uterine motility has been described in a previous communication. Some normal physiologic standards had been developed. It was thus relatively easy to adopt the human subject for the biologic test of the potency of ergot and its various constituents. Our patients were in their immediate puerperium, usually from the sixth to the eighth postpartum day. The experiment was begun about two hours after breakfast and continued for an average of three hours. Most of these patients were multiparas because the majority of primiparas has had perineal repairs which might be contaminated or broken down by the manipulation. It is interesting to note that we have had no untoward symptoms of any importance in over 200 patients in introducing the bag into the uterus and allowing it to remain there two to five hours. One may conclude that the careful vaginal examination of a normal puerperal woman at this stage in the postpartum period is almost without danger, providing a rigid technic is maintained.

No medication was given in most of our cases for at least one-half hour so that the normal uterine motility could be recorded. It is best to give only one drug to each patient, thereby avoiding confusing reactions. Normally, three types of uterine motility have been observed during the early puerperium. About 10 per cent of the patients had rather vigorous spontaneous uterine contractions which occurred every twenty to thirty seconds following the insertion of the bag. This type of uterus was not desirable for study of the effects of experimental medication. The second type of response was that in which moderate contractions occurred at irregular intervals of from five to fifteen minutes. The drug responses in this type of uterus will tend to exaggerate the normal reactions, but the pharmacologic index will be accurate.

The best "test patient" is one in whom no uterine activity can be recorded. This occurs in about one-half of the multiparous women during the postpartum period. The presence of the bag itself in the uterus rarely initiates spontaneous uterine motility. We have allowed a bag to remain in such an inactive uterus for as long as five hours without initiating noticeable activity. It may thus be concluded that the irritating effects of the bag in the uterus are not important.

#### RESULTS

It is not our purpose to enter into a description of the chemical investigation of the new active principle in ergot which we are about to describe, since this will be published elsewhere in the near future.

Our earliest efforts concern themselves with the complete isolation of all the desirable physiologic activity in the crude ergot. We shall call this preparation which contains all the oxytocic principles (alkaloidal as well as nonalkaloidal) the crude extract, but, in reality, it is a very fine, almost crystalline, powder. It is completely soluble in alcohol and all hydrophyllic solvents. It has no unpleasant properties characteristic of the fluid extract of ergot. This preparation was dissolved in alcohol and administered as such or given in the form of a capsule. The total amount of the drug administered in each instance was the residue from a 3 gm. sample of the crude drug.

Believing the commonly accepted idea that the physiologic activity of ergot resided in its alkaloids, we further separated the crude extract into an alkaloidal and a nonalkaloidal fraction, in the sense outlined above. Our first extract soon revealed that although we were successful in the almost complete extraction of the alkaloids, this fraction

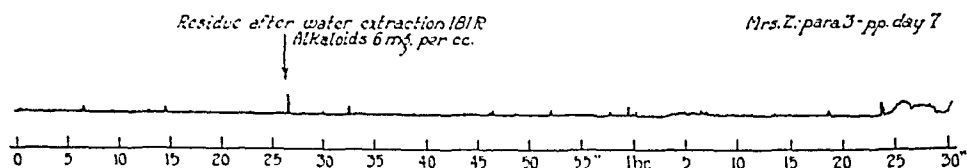


Fig. 1.—Tracing showing no uterine motility, even two hours after the oral administration of 3 c.c. of the alkaloidal fraction of the crude extract. This preparation assayed 6 mg. of alkaloid per cubic centimeter.

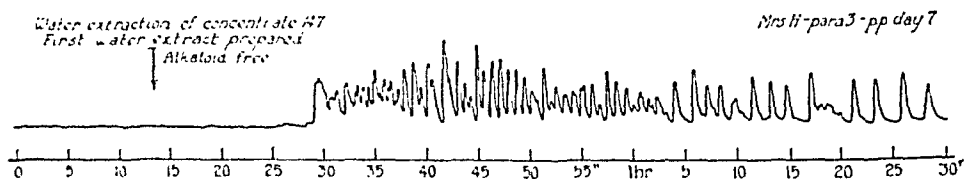


Fig. 2.—Tracing showing good uterine motility beginning fourteen minutes after the administration of the alkaloid-free fraction of the crude extract. This continued for over an hour. The concentrate numbers refer to the active principle obtained from different lots of ergots and by various chemical procedures.

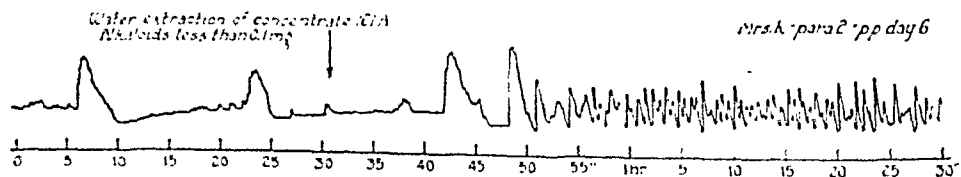


Fig. 3.—Tracing from a patient in whom there was moderate spontaneous uterine activity. Fourteen minutes after the administration of a second nonalkaloidal fraction a typical response was produced.

did not give the desired oxytocic activity. When we examined the residue which was almost free of alkaloids, according to the various tests, we were surprised to note that it was exceedingly active when tested on the human uterus according to our method previously described. Our interest was now focused on this interesting fraction. It usually represents 10 per cent of the crude extract, is water soluble, and practically

free from all the known ergot alkaloids. It was, therefore, impossible to assay this fraction by the colorimetric method of Smith since that method depends on those alkaloids. The Broom-Clark method (uterine strip) gave questionable results. The U.S.P. official cockscomb method, although being useful and giving some results, however, was found not to be entirely reliable in assaying this new principle. We then decided that in our future work the methods described for the human uterus were the only suitable ones for the study of our preparations.

The following typical graphs illustrate the reactions obtained from the various fractions of the crude extract (alkaloidal and nonalkaloidal).

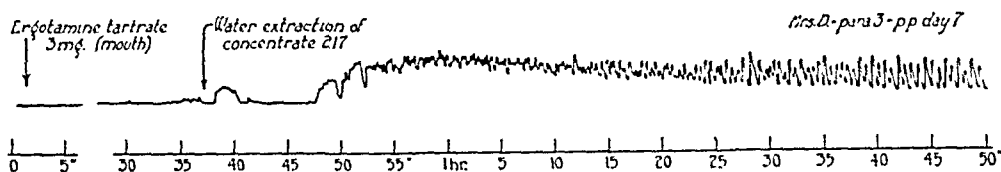


Fig. 4.—Tracing of uterine contractions, following the oral administration of 3 mg. of ergotamine tartrate forty-five minutes after the insertion of the bag. No uterine activity resulted up to forty-five minutes later, when 3 mg. of the new active principle was given, and produced a marked response within twelve minutes. Note the marked tetany and the frequency and amplitude of the contractions.

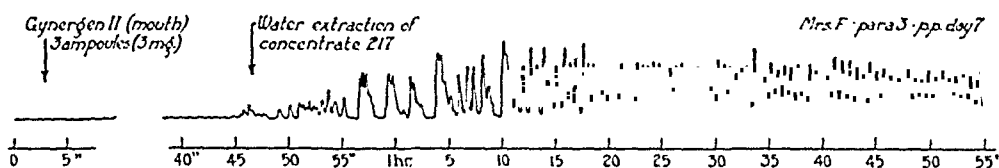


Fig. 5.—Tracing showing that for thirty minutes after the insertion of the bag no uterine motility occurred. Three ampoules of Gynergen II containing 3 gm. ergotamine tartrate were administered orally. There was no uterine response for a period of fifty minutes. Then 3 mg. of the new active principle provoked the typical response.

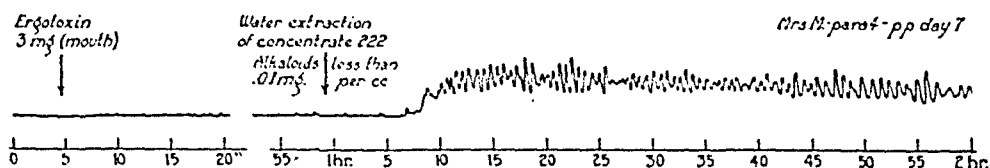


Fig. 6.—Tracing showing no uterine motility within one hour following the oral administration of 3 mg. of ergotoxin. Eight minutes after the administration of the active principle, containing less than 0.01 mg. alkaloids per cubic centimeter, produced a good response which continued for four hours.

The alkaloidal fraction assaying 6 mg. of alkaloids per cubic centimeter, when administered to the patient, showed no uterine motility at the end of two hours (Fig. 1).

The nonalkaloidal fraction was given to another patient and a good response was obtained fourteen minutes after its administration (Fig. 2). Here the curve is typical of what we shall refer to as a good ergot response.

A second nonalkaloidal fraction was administered to a patient and likewise provoked a good response fourteen minutes later. This uterus showed some spontaneous activity before the drug was given, but, nevertheless, resulted in the typical reaction (Fig. 3).



Having concluded that the nonalkaloidal residue was physiologically active on the human puerperal uterus, we next repeated previous experiments on the pure alkaloids derived from ergot. Ergotamine, ergotoxin, and sensibamine were given orally in 3 mg. doses. This dose is at least three times that recommended for therapeutic use. All of these pure alkaloids proved to be almost inert in these dosages. In each case the new active principle was given after the alkaloid failed to act within an hour, and an effective, prompt response was always obtained.

Ergotamine tartrate was given orally in a 3 mg. dose and no response was obtained forty-five minutes after the administration. This response is typical of an inactive type of puerperal uterus (Fig. 4). The alkaloid-free active principle provoked a prompt response within ten minutes, characterized by marked tetany which persisted longer than two hours. The contractions recurred rhythmically every twenty seconds and were of increasing vigor. The comparison in the effectiveness of the two preparations is most striking.

In Fig. 5, the patient received three double-strength ampules of Gynergen II orally. This dose contained the equivalent of 3 mg. of ergotamine tartrate. A response similar to the one above was obtained.

In Fig. 6, ergotoxin was administered orally in a 3 mg. dose. No response whatever was obtained at the end of one hour. A 3 mg. dose of the new active principle, containing less than 0.1 mg. of alkaloid, provoked the usual response within twelve minutes after administration.

Sensibamine administered orally in a 3 mg. dose likewise proved entirely ineffective in provoking uterine motility.

We may conclude that the pure alkaloids, when given orally in fairly large doses, proved to be inactive physiologically when tested on the human uterus. In each case the usual dose of the new active nonalkaloidal principle brought forth a very good response in ten to fourteen minutes. As may be seen from the curves illustrated, marked uterine tonus was present in every case. Uterine contractions recurred every fifteen to twenty seconds, and the induced activity lasted three hours or longer.

During the past year we have prepared a great number of extracts from the original crude nonalkaloidal fraction. The potency of these extracts was always carefully controlled by biologic assay on the human uterus. Having lost the most important index of pharmacologic activity, namely, the alkaloidal content, this method remained as the most feasible one. After long and tedious experimental methods, we finally arrived at an ingenious technic for rapidly obtaining our new active principle from the crude nonalkaloidal fraction.

We now have a new active principle of ergot as nearly free from alkaloids as is possible to determine by the various delicate tests. By the colorimetric test or the precipitant reagent mentioned previously, the total alkaloidal content per dose is less than one part in 100,000. This new active principle is soluble in water, alcohol and in most hydrophyllic solvents. It is relatively stable to heat. Many of our active preparations were boiled for thirty minutes without causing noticeable deterioration of the material. So far, our present observations would indicate that it is not very sensitive to the oxygen of the air,

so that preparations made in air are of potency equal to those prepared in vacuo. The active principle has been kept in a solid form for six months without showing signs of deterioration. The material may be obtained in a solid form by evaporation of the solution in vacuo. In solution it has a faint yellow color, and is tasteless and odorless.

The new active principle in its present form is agreeable and palatable. The dose is exceedingly small and may be dissolved in 3 c.c. or less of fluid. It produces no gastrointestinal or other undesirable symptoms in doses several times that required. It does not affect the pulse or blood pressure. When given orally the response is usually

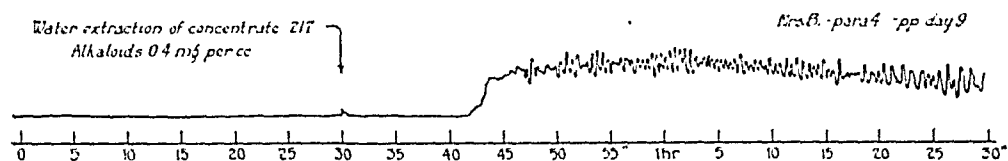


Fig. 7.—Tracing showing oxytocic activity of the nonalkaloidal fraction from Concentrate No. 217. This fraction assayed 0.4 mg. alkaloids per cubic centimeter. Two cubic centimeters of this active principle produced a good response beginning twelve minutes after its oral administration and continued for several hours until the bag was removed. Note the marked tetany which persisted throughout the experiment.

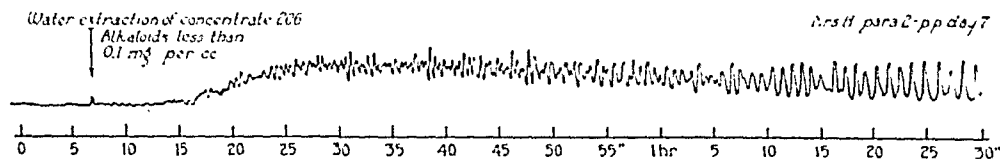


Fig. 8.—Tracing showing oxytocic activity of the nonalkaloidal fraction from Concentrate No. 206. This fraction assayed 0.1 mg. alkaloids per cubic centimeter and produced a typical reaction in ten minutes.

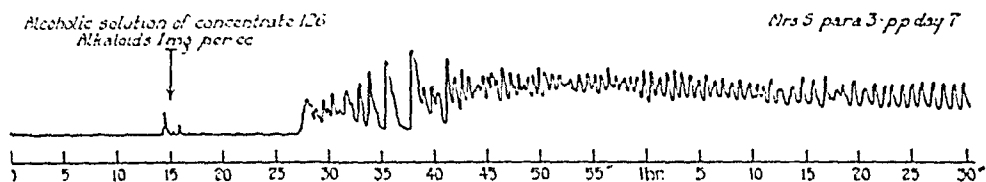


Fig. 9.—Response to an alcoholic solution of Concentrate No. 126. This preparation assayed 1 mg. per cubic centimeter of alkaloids. Although this fraction is high in alkaloidal content the response is no better than seen in other graphs.

obtained in six to fifteen minutes. Tetany is characteristic from the onset so that the excursions of the writing lever of the manometer do not return to the base line for one or two hours. This rise in the base line of the tracings indicates the uterine tonus. The contractions are vigorous and frequent, several per minute. The whole curve is entirely characteristic of a good response obtained from an active ergot preparation. The effect of the drug may continue for several hours or longer, but once the uterus is excited to activity, uterine motility rarely disappears completely as long as the bag remains in the uterus. As in the case of the usual preparations of ergot, this new material fails to provoke the general response following the use

of pituitrin. This interesting observation was made in our earlier work on ergot and is probably of extreme clinical importance. Koff, working on ergot at the Johns Hopkins University, made a similar observation which has not yet been reported. Pharmacologic antagonisms of this new principle are being studied at the present time.

The illustrations, Figs. 7 to 12, show the uniformity of the various responses in some of our patients following the administration of the drug. The numbers indicate the active principle in various nonalkaloidal fractions obtained by varying chemical processes. Furthermore, it has been found that many lots of ergot imported from various parts of the world contain variable amounts of this new principle. Undoubtedly, the amount of this new nonalkaloidal principle depends on the character of the ergot (Figs. 7 to 12).

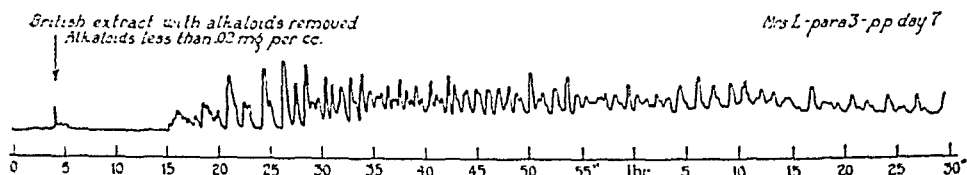


Fig. 10.—In this experiment the patient received 3 c.c. of the B.P. aqueous extract with the alkaloids removed so that it assayed less than 0.02 mg. per c.c. A fair response resulted.

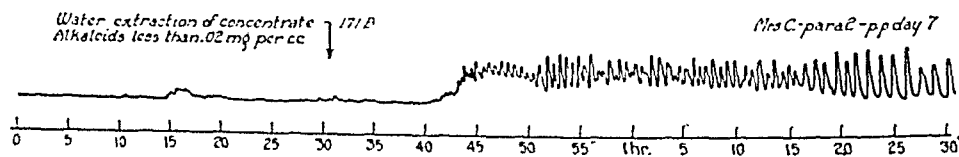


Fig. 11.

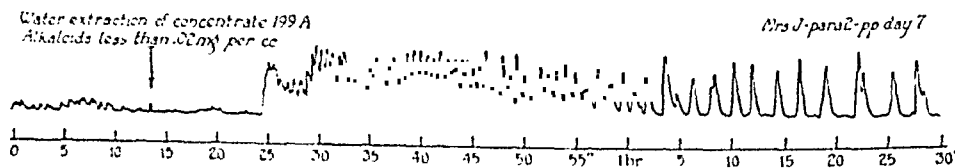


Fig. 12.

Figs. 11 and 12.—The responses to the administration of the new active principle in different types of patients. In both cases, although the preparations were obtained from different lots of ergot, the fractions assayed less than 0.02 mg. alkaloids per cubic centimeter. The motility appeared ten minutes after the drug was taken orally and continued for several hours. Note again the marked tetany produced, as well as the frequency of the uterine contractions.

The new active principle was usually given in 3 mg. doses in solid form, plain and salol-coated capsules, and in solutions. The various responses were accurately recorded on a synchronous kymograph for periods ranging from two to five hours. Thus far we have tested this new principle on more than 100 patients.

Chen and Swanson of the Eli Lilly Research Laboratories have controlled all of our work very closely by means of biologic assays on animals. The official cocksecomb method has not yielded reliable results when compared with the effect on the human uterus. A preparation of the new active principle remains active for the human uterus

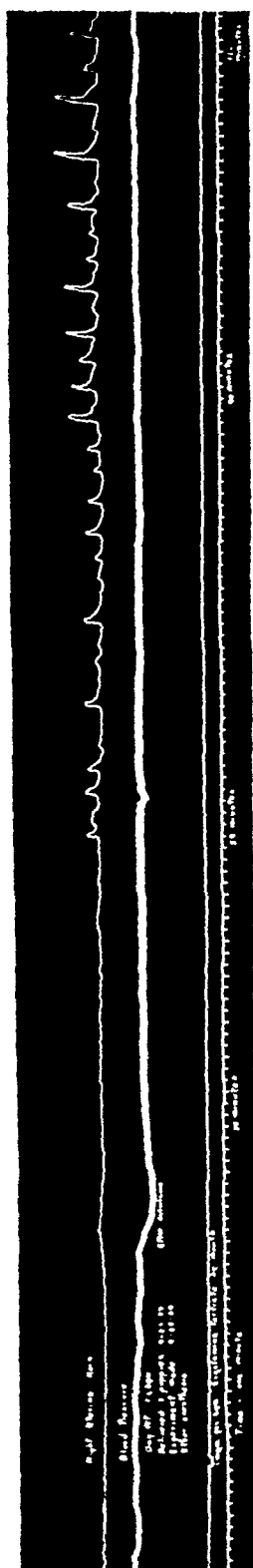


Fig. 13.—Tracing obtained from a dog on the third postpartum day; uterine contractions recorded by the insertion of a balloon in the uterine cavity. Blood pressures also recorded. Ergotamine tartrate, 1 mg. per kg., orally, required fifty-four minutes to produce a definite onset of action on the uterine movement.

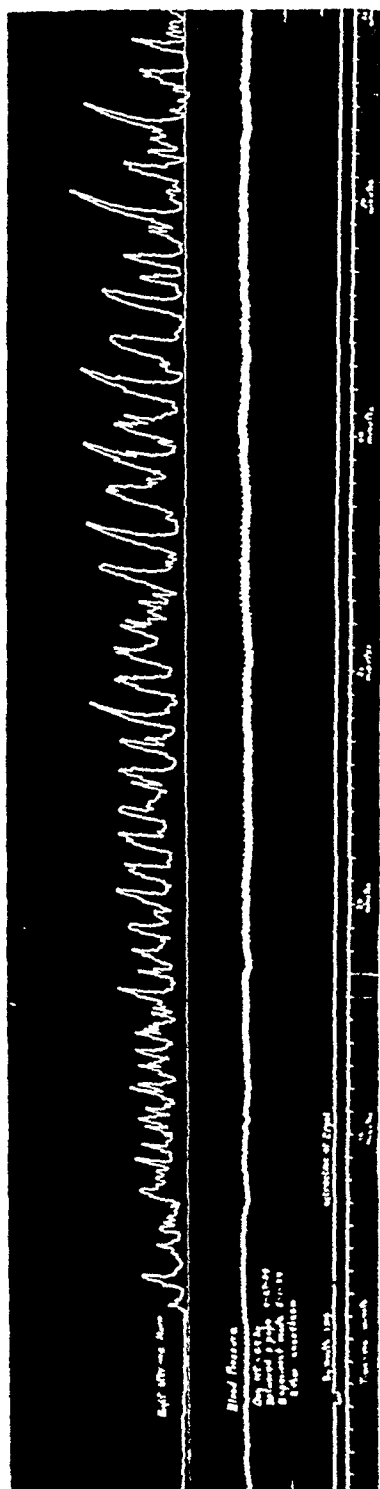


Fig. 14.—Tracing obtained from a dog on the fourth postpartum day; uterine contractions recorded by the insertion of a balloon in the uterine cavity. Blood pressures also recorded. Ergotoxin ethanesulphonate, 1 mg. per kg., orally, showed definite onset of action on the intact uterus in thirty minutes.

after it seems to have lost some of its effect on the cockscomb. The Broom-Clark method of assay is unreliable (Figs. 13 and 14).

They have placed small hydrostatic bags in the uterine cavity of dogs during the postpartum period and have corroborated all of our findings in human subjects. This experimental method may prove to be a desirable one for the biologic assay of this new active principle.

#### DISCUSSION

The new active principle in its present form meets all of the clinical needs of an oxytocic drug for use during the puerperium. The small dose given orally as a liquid or pill produces uniform uterine motility and tone which persist for three or four hours. Thus, the dose need not be repeated any oftener than three or four times daily. This uniform response is extremely important in ergot therapy. Its freedom from undesirable effects and its palatableness are likewise desirable. No evidence of undesirable reactions has been noted in doses three or four times the effective one. Our studies do not reveal any effect on the blood pressure either in animals or the human subject. The possibility of producing ergotism with gangrenous manifestations by the use of this drug has not been studied extensively. It is our impression that there is no danger of its occurrence even after the administration of large quantities. The desirable physiologic activity of this nonalkaloidal fraction is concentrated in so small a dose that little extraneous matter can be present. Clinically, this new active principle in its present form is entirely suitable for administration whenever the oxytocic activity of ergot is desirable. Because of the marked uterine tone produced by this active principle, its use, like that of other preparations of ergot,\* must be confined to the postpartum period.

Our own interest, however, continues to be centered on further purification and the determination of the exact chemical nature and formula of this interesting new principle. Problems of pharmacologic antagonisms are now being studied. When its molecular structure is learned, perhaps it will be found to resemble closely pituitrin.

#### CONCLUSIONS

1. Experimental evidence is presented to show that all the desirable physiologic activity in ergot does not reside in its alkaloids. The non-alkaloidal fraction has been proved to contain marked oxytocic activity when tested on the human postpartum uterus.

2. A new active principle has been isolated in the nonalkaloidal fraction of ergot which is active in doses of 3 mg. when administered orally. It does not give the usual precipitant reactions with reagents used in the tests for the known alkaloids in ergot. It has been esti-

\*The Eli Lilly Company have kindly consented to make large quantities for clinical assay, and have given it the trade name "Ergotoclin." This will provide ample material for extensive clinical observation.

mated that this new active principle, when isolated, contains less than 1 in 100,000 parts of the so-called alkaloids per 3 c.c. dose, the limit of chemical analysis.

3. The active alkaloids in ergot, ergotamine, ergotoxin, and sensibamine were given to patients orally in 3 mg. doses. No uterine responses followed within an hour. When this new active principle was administered orally a good characteristic response was noted.

4. The new active principle described was used in over 100 postpartum patients in which kymographic tracings of uterine activity were made for a period of three or four hours. The drug evokes a characteristic response in six to fifteen minutes after its administration. The uterine motility thus initiated persists for three or four hours. It is characterized by marked and persistent uterine tone and frequent uterine contractions. The curve is one which may be characterized as a good ergot reaction.

5. The usual methods of biologic assay were used to control the physiologic activity present in our new active principle. The Smith colorimetric assay is valueless. The official U.S.P. cockscomb method gave uncertain information. The Broom-Clark method was an unreliable index of its oxytocic activity. The best method of biologic assay for this new active principle is on the human postpartum uterus and on the postpartum uterus of the dog. The method of inserting a hydrostatic rubber bag for the study of uterine motility is entirely feasible in both cases.

6. The new active principle is palatable, odorless, faintly yellow in color, and is stable. It does not affect the blood pressure or provoke any undesirable reactions.

7. Present studies are under way on the purification and the determination of exact chemical nature and formula of this interesting new principle present in the nonalkaloidal fraction of ergot.

Since this work was reported the authors have succeeded in isolating the pure, active principle in crystalline form and have found it therapeutically active in doses of 0.1 mg. in the postpartum patient. Further chemical, pharmacologic and clinical work will be reported in the near future.

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# A CONSIDERATION OF THE SURGICAL MENOPAUSE AFTER HYSTERECTOMY AND THE OCCURRENCE OF CANCER IN THE STUMP FOLLOWING SUBTOTAL HYSTERECTOMY\*

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A SURVEY of the literature reveals disagreement concerning two important considerations in the life of individuals following hysterectomy. These concern the onset and character of surgical menopause after hysterectomy with and without ovarian conservation and the incidence of cancer in the cervical stump after subtotal hysterectomy. This report is part of a complete review of all hysterectomies performed at the University Hospital during the period 1901 to 1932 inclusive, and will be limited to a consideration of the two aspects mentioned above. The records of 2,042 hysterectomized patients were reviewed and a questionnaire sent to each. Six hundred and fifty three replies were received.

## SURGICAL MENOPAUSE AFTER HYSTERECTOMY

Inasmuch as Krieger<sup>1</sup> in a series of 2,991 cases, found that the menopause occurred spontaneously between thirty-six and forty years in 12 per cent, and Sessums and Murphy<sup>2</sup> found that it occurred before forty years in 5.2 per cent, we have purposely limited this part of our study to women thirty-six years of age or less. The upper limit of thirty-six years was chosen in order to avoid the inclusion of women who might be having a spontaneous early menopause. Two hundred and nine replies to our questionnaire were available for this purpose.

In the past it was generally conceded that removal of the ovaries was soon followed by menopausal symptoms. Little consideration, however, was given to the after-effects and end-results in patients following hysterectomy with ovarian conservation. Reports by Polak,<sup>3</sup> Sessums and Murphy,<sup>4</sup> Tamis,<sup>5</sup> Peterson,<sup>6</sup> Novak,<sup>7</sup> and Kelly<sup>8</sup> have indicated that the life history of the retained ovarian tissue is short and that menopause occurs at an earlier age in women operated upon than in women not operated upon. Most observers agree that hot flashes or flushes are the most constant tangible clinical evidence of menopause. We have also adopted this as our criterion and have taken the presence of this symptom as an indication of menopause.

\*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.

In our questionnaire we did not attempt to obtain information concerning the severity of the flashes because of the individual variation in response to subjective symptoms. Flashes reported as severe by one person might be considered mild by another. Since replies as to the severity of flashes would be of little statistical value, we limited our inquiry to the time of onset and duration of the symptom.

Table I serves to emphasize the contentions made by Abel and Zweifel,<sup>9</sup> Bailey,<sup>10</sup> and Sessums and Murphy concerning surgical menopause; namely, that a greater proportion of women develop symptoms of the menopause at an early age (forty years and under) after hysterectomy with ovarian conservation than in women who were not operated upon. The 57.5 per cent and 58.3 per cent for subtotal and total hysterectomy, respectively, noted in our series is much higher

TABLE I. INCIDENCE OF HOT FLASHES

OPERATION	TOTAL	WITH HOT FLASHES		WITHOUT HOT FLASHES	
		NO.	PER CENT	NO.	PER CENT
Subtotal hysterectomy with ovarian conservation	40	23	57.5	17	42.5
Subtotal hysterectomy with bilateral oophorectomy	109	97	88.9	12	11.1
Total hysterectomy with ovarian conservation	24	14	58.3	10	41.7
Total hysterectomy with bilateral oophorectomy	36	31	86.1	5	13.9

than that reported by Krieger (12 per cent) and by Sessums and Murphy (5.2 per cent). Table I also confirms the well-established fact that after removal of both ovaries most women develop evidence of the menopause: 86.1 per cent and 88.9 per cent for total and subtotal hysterectomies in this series. This marked difference in the incidence of women developing hot flashes after ovarian conservation and ablation would reemphasize the importance of conserving ovarian tissue whenever possible in order to prevent the onset of menopause as evidenced by hot flashes.

When we examine Table II we see that the average time of onset of hot flashes after the operation is considerably delayed in the subtotal hysterectomies. This would suggest the existence of some relationship between retained uterine tissue and menopausal symptoms. The exact nature of this relationship is not known. The fact, however,

TABLE II. AVERAGE TIME INTERVAL BETWEEN OPERATION AND HOT FLASHES

OPERATION	AVERAGE TIME OF ONSET (ALL OCCURRING BEFORE AGE 40)
Subtotal hysterectomy with ovarian conservation	18.0 months
Subtotal hysterectomy with bilateral oophorectomy	7.0 months
Total hysterectomy with ovarian conservation	14.5 months
Total hysterectomy with bilateral oophorectomy	2.25 months



that this time relationship holds even when both ovaries are removed, would suggest an endocrine function for the endometrium or cervix or both.

Our findings concerning the duration of hot flashes are at variance with those reported by Maxwell,<sup>11</sup> Graves,<sup>12</sup> and Bride.<sup>13</sup> They were of the opinion that the surgical menopause following complete removal of the ovaries, though more severe, was shorter. Tables III and IV show the average duration of hot flashes for each operative group as well as the percentage for each two-year interval. The higher average in our study may perhaps be explained on the basis that our series covers a period of thirty-one years, and the patients, therefore,

TABLE III. DURATION OF HOT FLASHES

OPERATION	AVERAGE DURATION OF HOT FLASHES
Subtotal hysterectomy with ovarian conservation	58.0 months
Subtotal hysterectomy with bilateral oophorectomy	78.0* months
	Corrected average 68.0 months
Total hysterectomy with ovarian conservation	92.0† months
	Corrected average 63.0 months
Total hysterectomy with bilateral oophorectomy	57.0 months

\*Includes two patients whose hot flashes had lasted twenty years and two patients whose hot flashes had lasted twenty-five years.

†Includes two patients whose hot flashes had lasted twenty years.

TABLE IV. DURATION OF HOT FLASHES

OPERATION	0-2 YEARS	2-4 YEARS	4 YEARS AND OVER
Subtotal hysterectomy with ovarian conservation	26.3%	22.7%	40.9%
Subtotal hysterectomy without ovarian conservation	24.1%	26.3%	49.4%
Total hysterectomy with ovarian conservation	16.6%	41.7%	41.6%
Total hysterectomy without ovarian conservation	30.7%	26.9%	42.3%

have been observed for a longer period after operation. The long average duration of symptoms in our series among the partially hysterectomized group without ovarian conservation is due to the fact that there were two patients whose flashes had persisted for twenty years and two for twenty-five years. If we exclude these four patients our average becomes 68 instead of 78 months. The same is true for the group having a total hysterectomy with ovarian conservation which included two patients who had had flashes for twenty years. Were these eliminated the average would be 63 instead of 92 months. We believe that the corrected averages are more representative of the true picture in each group and that they would indicate little difference in the duration of hot flashes between the two groups, i.e., with and without conservation of ovarian tissue.

RELATION OF PREOPERATIVE CONDITION TO POSTOPERATIVE  
OVARIAN FUNCTION

An analysis was also made of the possible relationship between the preoperative disease and the postoperative occurrence of hot flashes as suggested by Richardson.<sup>14</sup> Data on this relationship are shown in Table V. As pelvic inflammation and fibroids made up 74 per cent of the preoperative diagnoses, we analyzed these two groups only. Sixty-eight per cent of the patients with pelvic inflammation in whom ovarian tissue was conserved developed hot flashes before forty years of age, whereas this occurred in only 36.3 per cent of the patients operated upon for fibroids. Examining Table VI we see also that pelvic inflammation was the preoperative diagnosis in almost half of the patients with ovarian conservation who developed hot flashes.

TABLE V. PATIENTS THIRTY-SIX YEARS OR LESS WHO HAD HYSTERECTOMY WITH OVARIAN CONSERVATION SHOWING PERCENTAGE OF THOSE WITH AND WITHOUT HOT FLASHES FOR LOCAL DIAGNOSIS

PREOPERATIVE DIAGNOSIS	WITH HOT FLASHES	WITHOUT HOT FLASHES
Pelvic inflammation	68.0%	32.0%
Fibroids	36.3%	63.6%

TABLE VI. PREOPERATIVE DIAGNOSES IN THE PATIENTS THIRTY-SIX YEARS OF AGE AND LESS WHO HAD HYSTERECTOMY WITH OVARIAN CONSERVATION

DIAGNOSIS	PER CENT WITH HOT FLASHES	PER CENT WITHOUT HOT FLASHES
Pelvic inflammation	45.9	27.5
Fibroids	21.6	48.2
All others	32.5	24.2
Total	100.0	99.9

Inasmuch as pelvic inflammation necessarily presupposes some disease of the appendages either whole or in part, we might assume that the preexisting disease with destruction of ovarian tissue was responsible for the early development of menopausal symptoms. Any decision as to conservation should, therefore, take into consideration the status of the ovary or ovaries to be left in place. Even in young individuals if the ovaries show degenerative changes or evidence of infection, it would appear wiser to remove the appendages in order to prevent recurrence of pelvic symptoms, especially since our study shows the diseased ovary to be of little value in preventing menopausal symptoms.

EFFECT OF HYSTERECTOMY UPON LIBIDO

In many instances, from the patient's point of view, the maintenance of sex life assumes a far greater importance than the presence or absence of menopausal symptoms. Our questionnaire included information on this point. We did not attempt to evaluate the actual status

of the patient's sex life because so many other factors such as temperament and social adjustment of both husband and wife must enter into any such consideration. Our investigation dealt only with changes which occurred in libido after operation. The results for all age groups in relation to the nature of the operation are shown in Table VII. It will be noted that a greater percentage of women showed an increase in libido when the ovaries were conserved than when they were both removed. Those with complete removal of the ovaries, however, show no uniformity in regard to change in libido. Patients having a total hysterectomy and bilateral oophorectomy revealed the greatest decrease as might be expected but interestingly enough this did not prove true in patients partially hysterectomized with bilateral oophorectomy.

TABLE VII. EFFECT OF OPERATION UPON LIBIDO

OPERATION	TOTAL	NO CHANGE		INCREASE		DECREASE	
		NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Subtotal hysterectomy with ovarian conservation	162	74	45.67	28	17.28	60	37.04
Subtotal hysterectomy without ovarian conservation	249	130	52.21	22	8.83	97	38.95
Total hysterectomy with ovarian conservation	114	67	58.77	13	11.40	34	29.82
Total hysterectomy without ovarian conservation	113	51	45.13	9	7.96	53	46.90

TABLE VIII. CHANGES IN LIBIDO AFTER OPERATION IN RELATION TO HOT FLASHES

SEX ACTIVITY	PATIENTS WITH HOT FLASHES			PATIENTS WITHOUT HOT FLASHES		
	NO.	PER CENT	AV. AGE	NO.	PER CENT	AV. AGE
No change	191	45.0	39.0 yr.	126	60.0	41.2 yr.
Increased	50	11.8	36.9 yr.	23	10.9	37.5 yr.
Decreased	183	43.2	39.0 yr.	61	29.1	39.6 yr.
Total	424	100.0		210	100.0	

Study of change in libido in relation to the presence or absence of hot flashes (Table VIII) revealed that the presence of hot flashes was to a certain extent related to the libido of the individual. Thus 42.2 per cent of the patients with hot flashes who replied to the question concerning sex activity showed a decrease whereas only 29.1 per cent of those without hot flashes showed a decrease.

The fact, however, that 57 per cent of the individuals who developed hot flashes, which we have considered as evidence of the menopause, showed either an increase or no change in their libido, would seem to indicate that this function in the female is not entirely controlled by the pelvic organs, and their retention is not necessarily essential to the maintenance of a normal sex life.

## CARCINOMA OF THE CERVIX FOLLOWING SUBTOTAL HYSTERECTOMY

The second portion of this report deals with the occurrence of cancer in the stump following subtotal hysterectomy. The study is based on questionnaire replies returned by patients who had been partially hysterectomized, and in addition, includes a review of all the cases of cancer of the cervix seen at the University of Michigan Hospital from 1902 to 1932 inclusive. Only those patients who developed evidence of malignancy of the stump a year or more after operation were considered, for as von Graff<sup>15</sup> pointed out, a cancer that developed in the stump within the first year after the operation may be considered to have been present at the time of operation.

Examination of hospital records shows that 1,022 cases of cervical cancer have been seen in the gynecologic department during the period from 1902 to 1932. Of this number 18 occurred in the cervical stump, an incidence of 1.76 per cent.

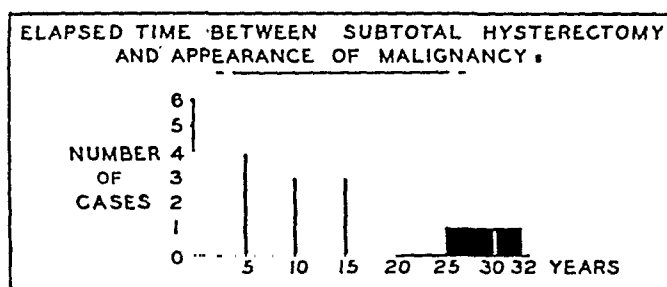


Chart 1.

The indications for these 18 subtotal hysterectomies are shown in Table IX. As noted, 11 or 61 per cent of the patients had been operated upon for uterine fibroids. Leonard,<sup>16</sup> Spencer,<sup>17</sup> and Polak<sup>18</sup> all point out that in the majority of the cases the original subtotal hysterectomy was performed for uterine fibroids.

Unfortunately no information as to the operative technic or the care of the cervix postoperatively to prevent later malignancy could be obtained, since all but one of the operations were performed outside the University Hospital.

TABLE IX. INDICATIONS FOR SUBTOTAL HYSTERECTOMY

Fibroids	11
Adhesions following pelvic abscess	1
Dermoid cyst of ovary	1
Vaginal bleeding (negative for malignancy)	1
Enlarged and inflamed uterus, no tumor	1
Unknown causes (30, 19, and 7 years before cancer)	3

The average elapsed time (Chart 1) between operation and the development of cancer was twelve years. The shortest interval was one and one-half years and the longest thirty-two years. In 77.7 per cent of the patients the cancer did not develop in the stump until after the sixth year. Of the 18 cases there were found to be

14 squamous-celled carcinomas, 2 adenocarcinomas, and 2 undifferentiated carcinomas. The average age of the patients when the cancer was diagnosed was 49.7 years; the youngest being thirty-six and the oldest sixty-seven. They were all American, 17 white and 1 colored.

Sixty-one (61.0) per cent of the cervical stump cancers were far advanced when diagnosed. Fourteen cases or 77 per cent of the patients died in an average time of ten months after the cancer was diagnosed, making an average of approximately thirteen years after the subtotal hysterectomy. Four patients are known to be living. Two of these have far-advanced malignancy and two have remained free from recurrence five and ten years, respectively, after treatment.

We believe that the method of determining the incidence of cancer in the stump by studying a group of cervical cancers cannot express with any accuracy its true incidence. Consequently, a questionnaire study was made of subtotal hysterectomies performed during the period from 1901 to 1932 with reference to symptoms of cervical cancer and actual diagnosis of cervical cancer. We realize the inadequacy of such a study, with its incomplete returns and absence of tissue examination, but it was hoped that a combined report might be more expressive than either one alone.

Of the 416 cases of subtotal hysterectomy who replied to the questionnaire only one patient stated that she had developed a cancer. She has returned to the hospital and was found to have a far-advanced medullary squamous cell carcinoma of the cervical stump. There were five others who stated that they had "tumors" and had symptoms compatible with cervical cancer. We are investigating these patients further, but as yet have been unable to ascertain whether these are positively cancers of the cervical stump. These six cases represent 1.44 per cent of the 416 questionnaires returned. This is approximately twice as large as several previous similar series mentioned by von Graff which averaged 0.62 per cent in 7,244 subtotal hysterectomies.

Since both of these methods of studying this problem have been considered to represent the incidence of cancer in the cervical stump as a point of interest, we averaged the two results in our series. We find that the percentage of cancer and probable cancer from the two series is 1.6 per cent.

#### SUMMARY AND CONCLUSIONS

1. A review of 2,042 hysterectomies of various types is presented from the point of view of questionnaire replies concerning surgical menopause, sex activity, and the postoperative incidence of cervical stump cancer.

2. Hysterectomy with ovarian conservation in women thirty-six years of age or less was followed by menopausal symptoms before forty years of age in 57.5 per cent and 58.3 per cent for subtotal and total hysterectomy, respectively.

3. The greater delay in the occurrence of hot flashes after subtotal hysterectomy would suggest some endocrine function for the retained uterine tissue.

4. Our study would indicate that complete removal of all ovarian tissue hastens the onset but does not shorten the duration of symptoms of the surgical menopause as has been previously contended.

5. The high incidence of menopausal symptoms following operations for pelvic inflammation would suggest that conservatism in this condition is unwise, if ovarian tissue showing degenerative changes is to be retained.

6. The onset of surgical menopause should not presuppose a decrease in or cessation of sexual activity, since 57 per cent of the patients in this series who developed hot flashes showed either an increase or no change in their libido.

7. A review of 1,022 patients with cervical cancer indicates that the condition occurs in the cervical stump after subtotal hysterectomy for benign causes in 1.76 per cent of cases.

8. In 416 patients with previous subtotal hysterectomy who replied to a questionnaire one proved case of cervical cancer and five probable cases were found, an incidence of 1.44 per cent.

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The organisms were found to be most virulent in the pregnant woman during the sixth month. This finding coincides with the clinical fact that pyelitis occurs most often during the sixth and seventh months.

At term the virulency may be even greater in some individuals.

JAMES M. PIERCE.

## THE COEXISTENCE OF UTERINE MYOMA AND FUNDAL CARCINOMA\*

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THE association of myoma and neoplasm of the uterus is not uncommon. Ellis S. Moeller reported 18 cases of myoma combined with sarcoma and 5 instances of myoma and fundal carcinoma. Twice he found myoma and cervical carcinoma in the same specimen. In some statistics the association with sarcoma seems to be even more frequent. Undstroemer reported among 769 cases of myoma 14 sarcomas but only one fundal carcinoma. Forgue found among 299 hysterectomies performed for myomas in six cases a coexistence of myoma and adenocarcinoma of the fundus. Other authors found the combination still more frequently; Scharlieb, two fundal cancers among 100 myomas; and Nicol Haultainmon, five fundal cancers among 120 myomas.

A study in our laboratory of 17,030 tissue examinations showed 531 myomas. In other words, 3 per cent of our tissue examinations concerned myomas. Fundal cancer and myoma were found together in 10 cases, 1.9 per cent of all myomas; while cervical cancer and myoma were found in one case, 0.19 per cent. The combination of myoma and sarcoma was found 12 times. This is an incidence of 2.3 per cent of all myomas.

We found in our material 40 fundal cancers, 10 of them combined with myoma. On the other hand there were 30 epitheliomas of the cervix and only one combined with myoma.

Piquand who has made a very thorough study of the relationship between myoma and carcinoma found among 3,230 myomas, 48 combined with carcinoma of the fundus, a percentage of 1.5. He was also able to show that among 166 fundal cancers 41 were combined with myomas, an incidence of 25 per cent. In his material among 600 women with uterus myomatousus, he found 9 carcinomas of the fundus and 12 of the cervix. Among 600 women without myomas there was one carcinoma of the fundus and three of the cervix.

These figures show that carcinoma was found more frequently in the myomatous uterus than in the normal uterus. The percentage of fundal carcinomas was very striking.

Winter found among 2,331 carcinomas of the uterus only 151 fundal carcinomas. In other words there were 15 cervical carcinomas for every fundal cancer. In the presence of myoma, however, he found among 131 cases of uterine cancer, 80

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fundal and 51 cervical cancers. Judging from these statistics it is quite evident that the proportion between the two types of cancer has changed.

Considering all these facts the question may be raised: Is there any etiologic connection between myoma and carcinoma, especially carcinoma of the fundus? In the literature, opinions disagree.

Cotte, for instance, thinks that myoma and carcinoma are entirely independent. Bland Sutton thinks that myoma may provoke the development of carcinoma. Winter believes that the connecting link between the myoma and carcinoma is hyperplasia of the endometrium. Piquand refuses to believe that we have to deal with a mere coincidence. He found "in almost all cases very marked alterations of the endometrium—thickening of the mucosa and a hypertrophy of all its elements, especially of the glands, which are distended and tortuous. Their number is considerably increased. Sometime, sooner or later, the proliferation becomes irregular, the cells fill out the lumen and invade the deeper tissues in the neighborhood."

Among our cases there are 25 in which the myoma was combined with adenoma, 4.7 per cent, and 17 with a combination of myoma and endometrioma, 3 per cent. It was possible to find a marked hyperplasia of the endometrium in 248 cases of myoma, an incidence of 47 per cent, while in 73 cases *no* hyperplasia of the endometrium was found, 14 per cent. In 140 cases of myoma the endometrium was either not studied or could not be studied because the uterus had not been removed.

Before discussing our cases we have to consider the conditions under which the carcinoma and myoma may be combined. In rare instances the carcinoma develops *in* the myoma. There are different possibilities. It is a well-known fact that a carcinoma cannot develop from the myoma itself, but there may be epithelial tissue present in the myoma from which the cancer develops. Embryonal debris of the wolffian body or of the canal of Mueller or some aberrant uterine glands may undergo cancerous changes. In unusual cases metastases from a remote cancer, namely the breast, stomach or intestine, may be found in the myoma.

In the majority of the cases the myoma first causes hyperplasia of the endometrium, then this changes into an adenoma and the adenoma into a carcinoma. Piquand quotes several cases of Eppinger and Maslowsky in which the adenoma was seen microscopically and after a few months it had changed into cancer. Piquand also thinks that calcification of the myoma acts more definitely as an irritating cause of cancer. He found the combination of calcified myoma and carcinoma in nine cases.

We were able to study such a case.

CASE 1.—Mrs. M. B., aged seventy-one years, married. There was no family history of cancer. She had never been ill or operated upon. Menopause began at fifty-four. She gave birth to two full-term children. A prolapse of the uterus had been present for eighteen years. For seven months there had been vaginal bleeding



and a foul yellowish brown discharge from the vagina. The patient was a slender, well-developed and well-nourished female. The pulse rate was 80, the blood pressure, systolic 170 and diastolic 90. The general physical examination was entirely normal. Gynecologic examination revealed an old laceration of the perineum with moderate cystocele and rectocele formation, and complete prolapse of the uterus. The uterus itself was about two-thirds normal size, regular in outline and freely movable. Both adnexa were normal.

Preoperative urinalysis was normal. Urea, urea nitrogen, and nonprotein nitrogen were 26.3, 12.3, and 23 mg., respectively.

The patient was operated upon by Dr. R. S. Cron, April 23, 1930. A Mayo type of complete vaginal hysterectomy and perineorrhaphy were performed. A Pessar retention catheter was left in the bladder. After an uneventful convalescence, the patient left the hospital on the fourteenth day, and at present is living and well.

The specimen was a senile uterus with a fundus the size of a plum. The cervix was 3.5 cm. long and showed many Nabothian cysts. In one corner of the uterus a hard mass the size of a cherry was found. In the opposite corner, just corresponding to the calcified mass on the other side, was a soft tumor of papillary structure the size of an olive. Invasion of the deeper layers was already visible. The color of the tumor was yellowish gray, the consistency very friable.

The microscopic examination shows a typical adenocarcinoma of the fundus: large cell strands in glandlike grouping. The cells are irregular in size and shape and show many hyperchromatic nuclei. Mitotic figures are uncommon. The stroma is invaded by polymuclear leucocytes.

A calcified myoma had provoked an adenocarcinoma on the opposite side.

CASE 2.—Mrs. R. S., aged sixty-one, married. No family history of cancer. Menopause at fifty-five. At the age of thirty-nine she gave birth to one child which was followed by phlegmasia alba dolens. In February, 1931, vaginal bleeding associated with a foul brownish discharge appeared. There was also a slight dull pain in the lower abdomen. The only other complaint was some dyspnea and palpitation with exertion and slight edema of the ankles.

The patient was medium built and well developed. The pulse rate was 80 and the blood pressure, systolic 180 and diastolic 100. The general physical examination showed evidence of early arteriosclerosis with cardiac hypertrophy. Gynecologic palpation revealed the uterus to be irregular in outline and enlarged to the size of a three months' pregnancy. The urine was normal.

On May 4, 1931, a diagnostic dilatation and curettage was performed by Dr. H. W. Shutter. The pathologist reported squamous stratified epithelioma of the fundus uteri. On May 7, 100 mg. of radium screened by hard rubber and brass were placed in the uterine canal for twenty-four hours. The above radium treatment was repeated on June 5, 1931. A total of 4,800 mg. hours of radium were administered within twenty-eight days.

On March 21, 1933, the patient was readmitted to the hospital after having had a recurrence of the bleeding for the past two weeks. There was still a uterine enlargement equal to the original findings. The arteriosclerosis and the cardiac enlargement had become more pronounced and the blood pressure was now 194 systolic and 100 diastolic.

On March 22, 1933, a total hysterectomy and left salpingo-oophorectomy were performed. The convalescence was rather stormy, the temperature rising to 102° for the first twenty-one days. On about the eighteenth postoperative day, pulmonary infarction of the left lung occurred. Oxygen therapy and supportive treatment were

effective and resulted in the patient leaving the hospital on the twenty-sixth post-operative day. At the present time the patient is enjoying good health.

The specimen in this case represented a large uterus the size of a grapefruit, weighing 305 gm. The cervix was 3 cm. long. Protruding into the uterine cavity was a tumor the size of a large chestnut. It was of soft consistency, edematous, and composed of interlacing reddish gray bundles. This was a myoma. On the opposite side of the uterus the endometrium was discolored, yellowish and greenish. The tumor showed distinct papillary structure and in some areas it was ulcerated. The growth continued to the upper right cornu of the uterus. The wall was 2 cm. thick and rather soft. In the posterior wall was a fibromyoma the size of a small olive. The tumor protruding into the uterine cavity consisted of interlacing smooth muscle bundles.

The fundus of the uterus was invaded by large strands of squamous stratified epithelial cells which were irregular in size and shape and showed mitotic figures.



Fig. 1.

Fig. 1.—Squamous stratified epithelioma of the fundus uteri. Line points to hornified strands of squamous stratified epithelium. ( $\times 600$ .)



Fig. 2.

Fig. 2.—Adenocarcinoma of the fundus. ( $\times 600$ .)

They corresponded in structure to the superficial layers of the epithelium, not to the basal cell type. There was distinct hornification. The stroma surrounding the epithelial cells was invaded by many polynuclear leucocytes.

The cervix did not show any gross lesions. Nevertheless, many sections were made but no pathologic lesions found. Therefore, we have to consider that the epithelioma of the fundus developed on the base of a metaplasia of the uterine mucosa from columnar into squamous stratified epithelioma.

Also in this case definite changes were provoked by a mechanical insult: the endometrium had been substituted by a squamous stratified epithelium and this had undergone cancerous changes in form of a typical epithelioma. A similar case is described by de Gery and Perrot.

CASE 3.—Mrs. C. S., aged fifty-two, widowed, no family history of cancer. She had never been ill or operated upon. The menses had never ceased although hot

flushes occurred two years ago. She experienced one pregnancy which resulted in a stillbirth. For the past two years there had been almost continuous bloody discharge which at times had been profuse. The discharge had never been of foul odor.

The patient was of large build, moderately obese. The pulse rate was 86, the blood pressure, systolic 206 and diastolic 126. The general physical examination was entirely normal excepting for a moderate cardiac enlargement. Gynecologic examination revealed a freely movable uterus the size of a three months' pregnancy. Preoperative urinalysis was normal.

The patient was operated upon by Dr. C. A. Evans, Oct. 2, 1933, at which time a very extensive supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. The convalescence was uneventful. She left the hospital on the thirteenth day. There is no evidence of a recurrence at the present time.

This specimen showed a fundus uteri, weighing 183 gm. There was a large polyp-like growth the size of a plum protruding into the uterine cavity. It was of soft consistency and grayish brown color with hyperemia in the periphery.

The uterine mucosa was substituted by soft friable tissue of papillary structure. The wall of the uterus was 3 cm. thick.

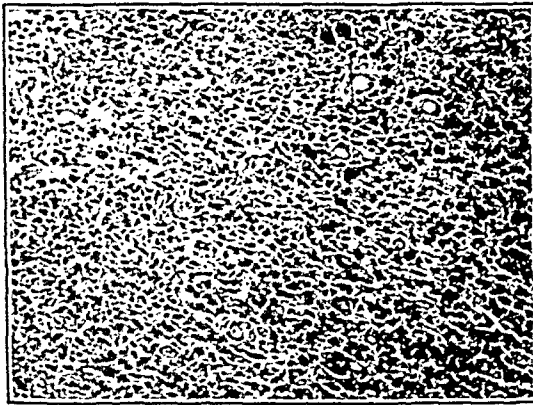


Fig. 3.—Polymorphous spindle-cell sarcoma going out from myoma. Lines point to giant cells.

Microscopic examination of the polyp showed a marked irregularity of the cells in size and shape. There were many spindle-shaped cells, irregular in size and grouped in whorls. Besides these there were large round cells frequently with hyperchromatic nuclei and also mitotic figures. Some of these cells showed several nuclei formed by incomplete cell division.

Diagnosis: Polymorphous spindle-cell sarcoma with giant cell formation.

On examination of the endometrium one found large strands of epithelial cells diffusely invading the tissues. Occasionally distinct grouping in glandlike formation remained, but frequently the cells were grouped in many rows so that solid strands of tissue were formed. The single cells were irregular in size and shape and showed occasional mitotic figures. There was a marked lymphocytic infiltration in the vicinity of the cancer cells.

Diagnosis: Adenocarcinoma of the fundus.

#### SUMMARY

Three cases of associated myoma and carcinoma of the uterus were described: (a) The first was a calcified myoma which provoked the growth of an adenocarcinoma on the opposite side. (b) The second

concerned a squamous stratified epithelioma extending from a metaplastic fundal mucosa. It was combined with a large submucous myoma. (c) The third was an adenocarcinoma combined with a submucous myoma which had undergone changes into a polymorphous spindle-cell sarcoma.

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## AMENORRHEA ASSOCIATED WITH BILATERAL POLYCYSTIC OVARIES\*

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ACCORDING to leading authoritative works on gynecology, the bilateral polycystic ovary is most commonly found in association with *uterine bleeding* (Fig. 1). This association has been recognized by the medical profession and is not infrequent in occurrence. Endometrial hyperplasia, multiple follicle cysts with granulosa cell lining, and a notable absence of corpora lutea in the ovary are the significant pathologic findings in such cases. The bleeding in these patients is readily explained by the fact that the increase in number of follicles lined by granulosa cells produces an excess of secretion of estrogenic hormone.

According to the same authoritative works, little or no mention is made of bilateral polycystic ovaries accompanied by *amenorrhea*, and inasmuch as we have encountered a series of cases exemplifying the latter conditions, we desire to present the results of our study of them.

Cyst formation in the follicular apparatus of the ovary is very common and is regarded to some extent as a physiologic process. When these structures are visible to the naked eye, they are regarded as cysts; when not, they are called follicles. When this process becomes excessive, persistent or progressive, the ovary becomes enlarged, tense, tender and painful, and produces what has been termed "cystic degen-

\*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.

eration of the ovary," and is usually bilateral. The exact cause of this formation is still in doubt; formerly, it was regarded as the result of inflammatory change due to either local infection or that from some distant focus. More recent observations and experiments point to an endocrine causal relationship of the polycystic changes in the ovaries. Furthermore, there are usually no adhesions or other gross or microscopic evidences of inflammation in the ovaries found in these cases. In the series of patients which we observed with bilateral polycystic ovaries and amenorrhea, the ovaries were found to be from two to four times the normal size and while they often maintained their original shape, they were sometimes distinctly globular. In one case, they were flat and soft, the so-called "oyster ovaries." The ovarian cortex was found to be hypertrophied in all of the cases and the tunica thickened, tough, and fibrotic.

The cysts were follicle cysts, near the surface, and almost entirely confined to the cortex, and they contained clear fluid. There were

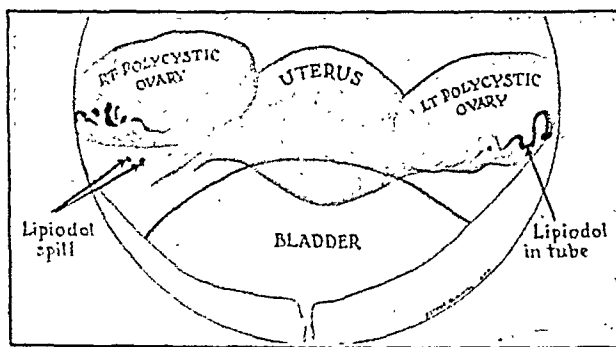


Fig. 1.

from twenty to one hundred cysts in each ovary, varying in size from 1 mm. to about 1.5 cm., but rarely larger. The color of the ovary was oyster gray with bluish areas where the cysts were superficial and appeared on the surface as sago-like bodies. On section, the variation in size of the cysts and the clear fluid contents were revealed. Corpora lutea were sometimes absent and when found, they were very small and deeply placed.

The uteri in these patients were either normal in size or smaller and firmer than normal. The remaining changes observed were those involving the secondary sex characteristics. The breasts presented no characteristic changes except in cases of long-standing amenorrhea when they were small, firm, and pale.

In some patients, there was observed a distinct tendency toward masculinizing changes. A typical rhomboid hairy escutcheon, hair on the face, arms, and legs, and coarse skin was noted. No voice changes have been observed by us. The external genitals in most

patients were normal, but in some, the labia minora and clitoris were markedly hypertrophied. Libido is apparently not affected by the changes noted in the ovaries.

### CASE REPORTS

CASE 1.—M. G., aged twenty-two, married one and one-half years, gravida 0, was first seen Oct. 3, 1928. Her chief complaints were sterility and amenorrhea. Menses began at age of thirteen, irregular, two to seven months, five-day duration, moderate, no pain. She was treated with estrogenic preparations, intramuscularly; she then menstruated irregularly every six or eight weeks; small doses of thyroid extract and calcium were given.

November, 1929: Menstruated about every seven weeks. Examination revealed moderate obesity and slight struma. Bimanual examination: Uterus was 2° retroverted, normal size; right ovary palpable and cystic. January, 1930: Transabdominal pneumoperitoneum (Fig. 2), revealed bilateral cystic ovaries, each ovary appearing as large as the uterine fundus. Operation: May 2, 1930, laparotomy. Uterus was small and both ovaries were polycystic and enlarged, the right more so than the

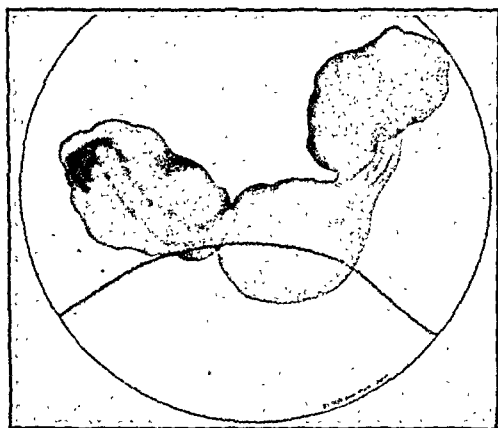


Fig. 2.

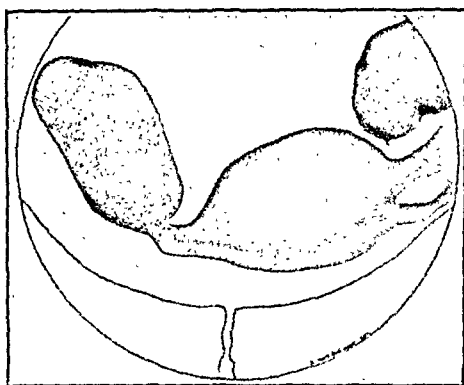


Fig. 3.

left. The left also contained a small fibroma. Wedge-resection of both ovaries. Uneventful recovery; discharged from the hospital on the twelfth postoperative day.

Forty-eight hours after operation, slight uterine bleeding occurred, and normal menstrual periods occurred monthly thereafter. Patient became pregnant in October, 1930, and again in February, 1933; both pregnancies were carried to full term and delivered normally. Menstruation since confinement is entirely normal, every twenty-eight days. August, 1934: Follow-up examination showed the uterus and both ovaries to be normal.

*Pathologic Report.*—Gross: Sections from both ovaries showed numerous cystic cavities varying from 1 mm. to 1 cm. in size. Ovarian tunic was thickened and fibrous. Microscopic: Thick tunic, many cysts varying in size, lined by theca cells; one normally developing graafian follicle; corpus albicans; old corpus luteum; tortuous and dilated blood vessels.

CASE 2.—B. K., aged twenty-nine, married five years, gravida 0, was admitted to the hospital Aug. 10, 1931. Her chief complaints were sterility and amenorrhea. Menses began at the age of fifteen, were irregular for several months; no menses for eight years prior to first examination. Menstruated twice last year (under our observation) after treatment with estrogenic hormone, intramuscularly. Phys-

ical examination: Rigid type; tight coarse skin, hairy face, arms, and legs; masculine escutcheon. Transabdominal pneumoperitoneum; bilateral cystic ovaries almost as large as uterine fundus (Fig. 3). Operation: Wedge-resection of two-thirds to three-fourths of each ovary. Uneventful recovery. Discharged from hospital on thirteenth postoperative day.

Patient has menstruated regularly every twenty-eight days since operation. Follow-up examination in May, 1933: uterus and both ovaries normal; secondary sex characters evidence little improvement; no pregnancy to date.\*

*Pathologic Report.*—Gross: Thick tunic, numerous cystic cavities up to 1 cm. in diameter near surface of ovary (Fig. 4). Microscopic: Tunic thick and fibrous; numerous cysts varying in size, lined by hypertrophied theca layer. Granulosa cells were scarce. Small (old) corpora albicantia. No corpora lutea.

CASE 3.—L. C., aged twenty-one, married two years, gravida 0, was first seen April 24, 1929. Her chief complaints were amenorrhea and sterility. Menses began at the age of thirteen, were always irregular, one- to nine-month intervals, usually six months, lasting for five or six days, scant; no pain. Treatment was

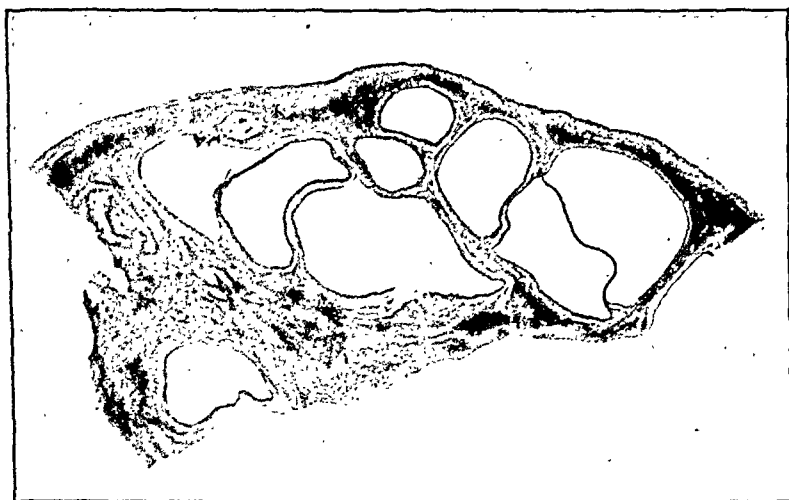


Fig. 4.—Photomicrograph (6 diameters) of section of wedge removed from ovary (Case 2).

given over a period of four years with estrogenic hormone preparations, intramuscularly, and thyroid extract by mouth. In December, 1929, patient had x-ray stimulation of ovaries with no results. In October, 1931, she became pregnant, and was delivered of a normal child at term, August, 1932. Following this, she had four normal periods at regular intervals followed by amenorrhea of one year and nine months. During this time, she was treated with estrogenic hormone preparations without benefit. Examination revealed a short, well-proportioned young woman; breasts normal, masculine escutcheon, long labia minora and hypertrophied clitoris. Bimanual examination showed normal sized uterus, both ovaries enlarged, globular and tender.

July 6, 1933: Transabdominal pneumoperitoneum and intrauterine lipiodol instillation showed both ovaries enlarged and elongated; tubes patent. Uterine contour was normal (Fig. 5). Oct. 14, 1933: Operation: Bilateral wedge-resection of about three-fourths of both ovaries, each of which was 5 by 7 cm. in diameter; the capsule was very thick and leathery. Uneventful postoperative course; discharged from hospital on twelfth day. Patient menstruated forty-eight hours after opera-

\*This patient is now (Jan. 30, 1935) three months pregnant.

tion and has had regular monthly periods for the past year. Check-up examination in September, 1934, showed the uterus and both ovaries normal to palpation.

*Pathologic Report.*—Gross: Thick tunica; numerous cysts up to 1 cm. in diameter. Microscopic: Moderately thick tunica; numerous cysts, some lined with granulosa cells, others with theca cells; some corpora albicantia; no corpora lutea; tortuous, large and thickened blood vessels.

CASE 4.—H. W., aged twenty-three, married three years, gravida 0, was first examined Jan. 3, 1933. Her chief complaints were sterility and amenorrhea. Menses began at the age of fifteen, were irregular, one to six months, usually three to four months; three- to four-day duration; profuse with clots and cramps. Last menstruation occurred six months previous to admission. No contraception for two years. Treated with estrogenic hormone intramuscularly and orally. Examination: Patient was large, obese with feminine escutcheon and large flabby breasts. Uterus normal; palpable left ovary was enlarged and cystic. Feb. 15, 1933: Transuterine pneumoperitoneum and lipiodol instillation showed the uterus to be normal in size; both ovaries were enlarged and cystic; fallopian tubes were patent (Fig. 6). Mar. 11, 1933: Operation: Bilateral wedge-resection of ovaries which were so large that

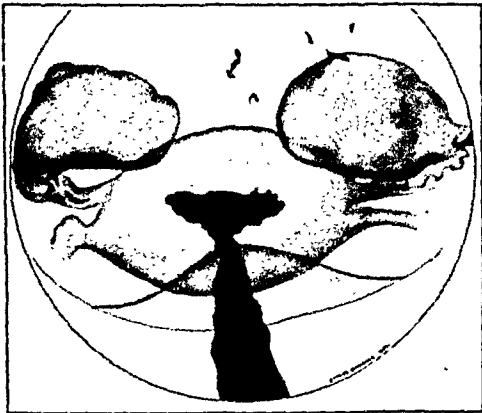


Fig. 5.

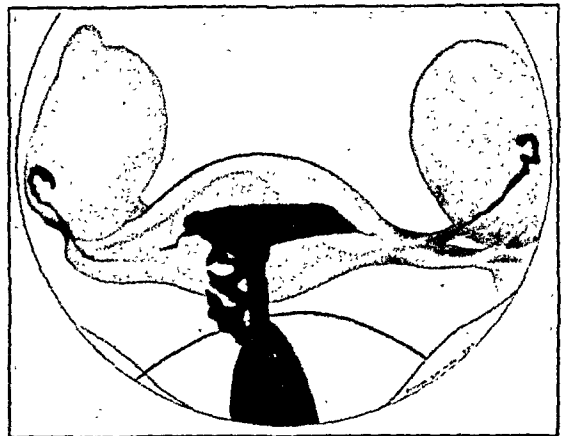


Fig. 6.

more than three-fourths of each was removed, leaving the hilus approximately the size of a normal ovary.

The patient made an uneventful recovery and was discharged on the tenth post-operative day. She menstruated on the sixth day and regularly every twenty-eight days thereafter for the past year and one-half. Bimanual examination in March, 1934, revealed a normal genital status.

*Pathologic Report.*—Gross: Each section showed several cysts up to 1.5 cm. in diameter. Microscopic: The ovary appeared normal; tunica moderately thickened and below were multiple small cysts; some lined with granulosa cells, others with theca cells. Normal cystic follicles; small corpora albicantia; cluster of granulosa cells evidently the edge of a normal follicle. No corpora lutea. In one portion was a small papillary cystadenoma. Tortuous and thickened blood vessels.

CASE 5.—O. B., aged twenty-five, married one and one-half years, gravida 0, was first seen in the clinic Jan. 9, 1933. Her chief complaints were irregular menses and sterility. Menses began at the age of fifteen, two- to three-month intervals, painful, duration three days. Last menstruation Dec. 29, 1932. Examination: Male escutcheon, hairy thighs, breasts normal. Bimanual: Cystic swelling of right ovary palpable, but not left. Uterus was small. Transuterine pneumoperitoneum and lipiodol instillation: Both ovaries cystic; right larger than left; tubes patent to gas



and filled with lipiodol (Fig. 7). Operation: Wedge-resection of one-half to two-thirds of both ovaries which were polycystic; the uterus was found to be small, firm, and slightly bicornuate.

Uneventful postoperative course; patient was discharged on the tenth day. Menstruation occurred on the fourth postoperative day, and regularly each month thereafter. Follow-up examination in September, 1934; uterus and ovaries found normal on palpation.

*Pathologic Report.*—Gross: Thick tunica; numerous cysts varying in size up to 1.5 cm. Hemorrhagic stroma. Microscopic: Moderately thickened tunica; recent corpus luteum with hemorrhagic corpus luteum cyst; many cysts lined by theca cells. Large corpus albicans; edematous vascular stroma with hemorrhage.

CASE 6.—E. A., aged thirty-three, married fifteen years, gravida ii, was admitted to the hospital Oct. 23, 1933. Her chief complaints were irregular menses for nine years, abnormal hairy growth for three years, and pain in groin for three years. Menses began at the age of twelve, regular until ten years ago, since then, five- to nine-month intervals, becoming longer. Menses were scant, lasting three or four days with no pain. Hairy growth on face, back, arms, and legs for past three years,

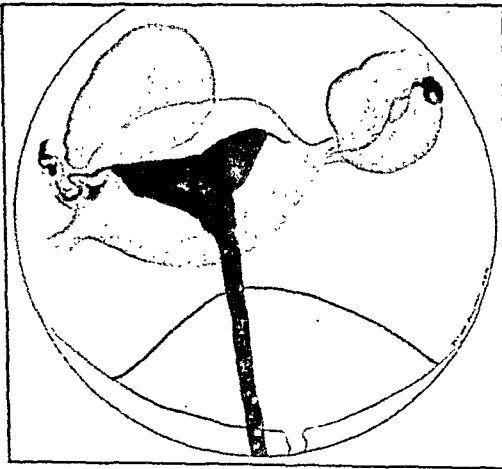


Fig. 7.

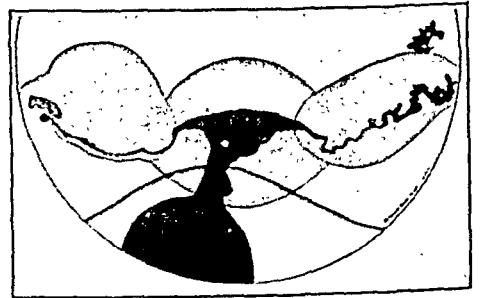


Fig. 8.

becoming more noticeable. Pain in both lower quadrants for three years, with lower abdominal pain accompanying the menstrual melenia even in the absence of bleeding. Gained 15 pounds in past year; weight, 175. Examination: short, obese, male escutcheon, hair on body and face; pendulous breasts. Uterus normal in size; both ovaries enlarged, cystic, tender. Transuterine pneumoperitoneum and lipiodol instillation: Both ovaries were enlarged, uterus was normal, and fallopian tubes were patent (Fig. 8). Operation: Bilateral wedge-resection of about one-half of each ovary, which contained multiple cortical cysts.

Uneventful recovery, discharged on thirteenth postoperative day. Uterine bleeding occurred on fifth postoperative day and menstruation recurred monthly thereafter (eleven months). Follow-up examination in June, 1934: No evidence of reformation of cysts, genital status normal.

*Pathologic Report.*—Gross: Thick tunica; numerous cystic cavities varying in size up to 1.5 cm. Microscopic: Tunica thickened in some sections and normal in others. Normal follicle with maturing ovum near surface. Large theca cyst with corpus albicans; recent corpus luteum.

CASE 7.—M. B., aged twenty, single, was admitted to the hospital Aug. 29, 1933. Her chief complaints were amenorrhea and pain in both lower quadrants for one

year. Menses began at fourteen years of age, always irregular, six weeks to four months, usually two months, seven-day duration, moderate, occasional clots, no dysmenorrhea. Physical examination revealed a tall, thin girl, with muddy complexion; facial acne; scant breast development. Rectal examination showed the uterus to be erect, and of normal size. The left ovary was cystic and from 7 to 8 cm. in length. The right ovary was cystic and 5 cm. long. Transabdominal pneumoperitoneum on Aug. 30, 1933. Bilateral polycystic ovaries, each as large as the normal uterine fundus (Fig. 9). Operation: Wedge-resection of the cystic portion of each ovary. Patient made an uneventful recovery and was discharged from the hospital on the ninth postoperative day. Menstruation has been regular since operation, and pain has been relieved. Patient was married a few months after operation and has remained in good health. She has moved to a distant city and reported in October, 1934, that she was in good health and that menstruation had recurred monthly.

*Pathologic Report.*—Gross: Sections of ovaries showed numerous cysts; and hemorrhagic and edematous stroma. Microscopic: Moderately thickened tunica; large corpus luteum cyst; numerous cysts lined by theca cells; follicle cysts with granulosa cell lining. Corpora albicantia; dilated blood vessels and very vascular stroma.

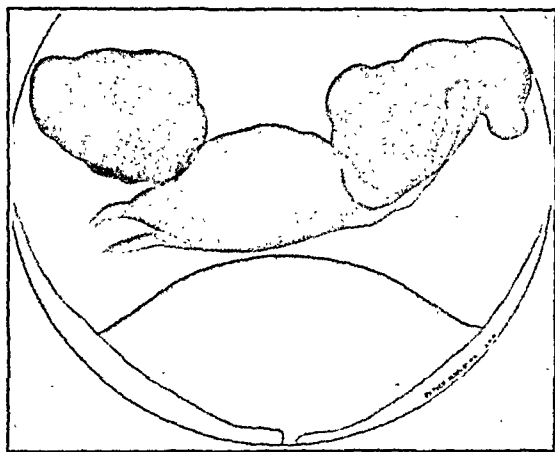


Fig. 9.

#### DIAGNOSIS AND TREATMENT

The diagnosis of polycystic ovaries is made only after careful and repeated examinations. The history of irregular menses with or without pain gives little clue to the ovarian condition and a bimanual or rectal examination may not always reveal the presence of polycystic ovaries. Due to the fact that the ovaries often show transient enlargements incident to physiologic changes, one must not arrive at hasty judgments. Furthermore, in cases of flat "oyster ovaries," it is sometimes difficult to palpate the pathologic enlargement. Conflicting opinions are not infrequent concerning the presence of these swellings.

The diagnosis is greatly enhanced in cases of ovarian swellings by the use of pneumoroentgenography, as one of us has previously described. We have been able to demonstrate the bilateral ovarian enlargements by this method when palpatory findings were doubtful or

disputed. The shadow of the normal ovary usually appears on the film to be about one-fourth of the size of that of the uterine corpus. When the ovary is polycystic, it appears from three-fourths to as large as the uterine shadow. This method of diagnosis has been of especial value when there was a difference of opinion concerning the presence of ovarian pathology. The film evidence is convincing as may be seen in the accompanying illustrations. After using pneumoroentgenographic diagnosis for more than ten years, we feel that we are qualified to endorse it as a most valuable aid in gynecology, and especially so in recognizing relatively small ovarian swellings which may escape detection on bimanual examination.

The treatment of amenorrhea and sterility in the group of patients under consideration was at first conservative, using endocrine preparations; eventually the treatment became surgical. In some of the earlier cases, injections of various endocrine preparations were made in an effort to adjust the menstrual cycle. Estrogenic hormone preparations which were reputed to be more or less potent were administered intramuscularly. Uterine bleeding occurred as a result of this treatment in some instances, but it is impossible to say whether this was true menstruation or anovular bleeding. At any rate, no lasting restoration of function followed these treatments and no pregnancies occurred. The use of anterior pituitary-like substances was avoided in order that a cystic change in the ovaries might not be thereby provoked, for, as Zondek has shown, hyperhormonal amenorrhea with overstimulation of the graafian follicles can be produced by the injection of prolan.

In the patients referred to in this series, we have resected from one-half to three-fourths of each ovary by wedge-resection, thereby removing the cortex containing the cysts, and have sutured the hilus with the finest catgut. The immediate results have been entirely satisfactory. All of the patients recovered uneventfully, and were discharged from the hospital from the ninth to the thirteenth postoperative days. Uterine bleeding occurred on the third to the fifth postoperative day and menstruation occurred monthly thereafter in every case. Our first patient, operated upon four years ago, has given birth to two children since operation.

#### DISCUSSION

The ovarian change in bilateral cystic ovaries is most probably a *result* of some hormonal stimulation and very likely relates to the anterior lobe of the pituitary gland. Geist reported fifty cases in which "antuitrin-S" was injected in large doses a few days prior to operation for fibroids. At operation, the ovaries showed definite changes. While the follicles did not grow in size, they were greatly increased in number. Geist described the additional changes in the ovary which

varied in intensity in direct relationship to the amount of hormone injected. He quotes the work of Mandelstamm and Tschackowsky who likewise produced polycystic ovaries in women by the use of anterior pituitary-like substances.

Oddly enough, the surgical treatment directed to the ovary in our series adjusted the endocrine balance to the extent of restoring normal menstruation and the reproductive function. Theoretically, one would expect that if the cystic portion of the ovary were removed without also removing the abnormal stimulus which produced the ovarian change, the same factors would still be operative, resulting in reformation of the polycystic change. Thus far, this has not been our experience although we have observed our patients over a period of from one to four years since operation.

Whenever one attempts to correlate the function or dysfunction with the structure of any of the endocrine glands, one is apt to encounter grave difficulties, due to the recognized instability of the normal anatomy of all glands of internal secretion. The association of amenorrhea with polycystic ovaries in our series is no exception to this statement. The pathologist is unable to conclude from a study of the sections taken from the ovaries in our patients that amenorrhea was a symptom. He can demonstrate no anatomic structure or characteristic change in the ovary which enables him to describe the clinical picture. The only consistent pathologic finding is the presence of follicle cysts lined by theca cells (Table I). The fact remains, however, that when we remove the cystic portion of the ovaries which to all appearances are the same as those observed in patients with uterine bleeding, normal function is restored to the sex apparatus.

It is unlikely that polycystic ovaries are congenital for the condition develops as a rule after the patient has menstruated more or less regularly for a period of years. The amenorrhea is usually secondary. It is also unlikely, for reasons stated above, that the multiple cyst formation is explained on the basis of inflammatory change. That hormones play a rôle in the polycystic change in the ovaries is extremely plausible in the light of our present-day conception of sex physiology. Whether it results from an excessive production of anterior pituitary sex hormone or not is debatable.

It is reasonable to assume that a *mechanical* factor operates actually to produce the most significant symptoms, namely: amenorrhea and sterility. The overproduction of cystic follicles which crowd the ovarian cortex but which do not rupture on the surface of the ovary, together with the presence of a thickened tunica, prevents the immature follicles from ripening and reaching the surface. It is possible that some of these follicles develop, and being impeded in their pathway to the surface of the ovary, may rupture into the cysts. We have ob-

TABLE I. BILATERAL POLYCYSTIC OVARIES WITH AMENORRHEA. HISTOPATHOLOGIC FINDINGS

	TUNICA	STROMA	BLOOD VESSELS	NORMAL FOLLICLES	FOLLICLE CYSTS		CORPORA LUTEA	CORPORA ALBICANTIA	TUMOR
					THECA	GRANULOSA			
1	Thick		Tortuous Distended	Few	Many		Recent	Many, old	
2	Thick		Tortuous Thick		Many	Few		Few, old, small Few, small	
3	Thick		Tortuous Distended		Many			Many, small	
4	Normal to moder- ately thick		Hyperplasia	One in section	Many	Few	Recent with c.l. cyst	Large, recent	Early papillary cystadenoma
5	Moderately thick	Edematous Vascular			Many	Few	One, recent	Many	
6	Normal to moder- ately thick			Few	Many		c.l. cyst	Many	
7	Moderately thick	Vascular	Dilated		Many				

served, in one of our sections, a normal maturing follicle just below and adjacent to a thin-walled theca cyst, so situated that if the follicle ruptured at all, its contained ovum would be discharged into the cyst cavity. This may account for the finding of small corpora lutea and albicantia even in the absence of menstruation. Ordinarily no corpora lutea would be formed unless the graafian follicles reached the surface of the ovary and ruptured. In further substantiation of the mechanical theory, we observed that by removing the cystic cortex which formed the barrier, physiologic function was restored. Apparently the incisional scar in the ovary is of no significance.

#### SUMMARY AND CONCLUSIONS

1. A series of seven cases is herewith reported in which amenorrhea was associated with the presence of bilateral polycystic ovaries.

2. Bilateral polycystic ovaries are most likely the result of hormonal influences and not the result of inflammatory change.

3. The diagnosis of ovarian pathology is greatly facilitated by the use of pneumorocentgenography.

4. The treatment of the amenorrhea with estrogenic hormone in the patients referred to proved unsatisfactory.

5. Surgical treatment, consisting of wedge-resection of the cystic cortex of the ovaries, was successful in completely restoring physiologic function. Menstruation in every instance became normal and remained so during the period of observation. Pregnancy followed in two patients.

6. It is our belief that a mechanical crowding of the cortex by cysts interferes with the progress of the normal graafian follicles to the surface of the ovary. This mechanical factor may account for the symptoms of amenorrhea and sterility.

7. Recurrence of the polycystic change in the ovary was not found in the follow-up examinations in any of the patients in this series.

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## THE OUTCOME OF PREGNANCY COMPLICATED BY UTERINE FIBROMYOMA\*

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THIS report deals with the observation and conduct of 97 pregnancies occurring in uteri harboring myomas, the presence of which was of clinical significance. The words "of clinical significance" are used to describe those myomas which, because of size, situation, or condition were a potential or actual cause of any of the following complications: pain, red degeneration or necrobiosis, bleeding, dystocia, and threatened abortion resulting from impaction of the myoma and the uterus in the pelvic cavity. In this study, 297 cases of pregnancy with fibromyoma were reviewed, in 97 of which the growths were classified as clinically significant. With the exception of those patients who underwent hysterectomy or myomectomy early in pregnancy, all patients in this series had about reached the twenty-sixth week of gestation, the so-called period of viability of the fetus.

The incidence of fibromyoma complicating pregnancy is difficult to estimate, since many of the smaller tumors, which are not situated on the anterior surface of the uterus, may be unrecognized both during pregnancy and labor. Various authors differ somewhat on statistics of the frequency of clinically significant fibromyomas during pregnancy.

Seipidas found 75 pregnancies in 985 cases of myomatous uteri, whereas Kelly and Cullen found only 11 in 1,674 operations for myoma. Troell was able to find only 20 cases of myoma among 5,129 puerperal women. Pierson gave a corrected incidence for pregnant women with fibromyomas of 0.6 per cent; Campbell reported 0.43 per cent. Watson gave an incidence of 1.3 per cent but stated that 40 in his series of 150 were doubtful. Spencer stated that fibromyomas occur once in every 150 pregnancies.

At the Mayo Clinic, the incidence of clinically significant uterine myomas in the total number of confinements is 1.9 per cent, which is higher than that of other observers. Many of these patients came to the clinic because of this specific complication, which perhaps explains the higher incidence. One per cent or less may be a more correct estimate of the entire country.

\*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, New Orleans, La.

Many uterine myomas complicating pregnancy do not produce symptoms, and only 44 of the patients in this series were aware of the presence of a tumor; 24 had had a previous diagnosis of fibromyoma elsewhere. Pain was the principal symptom, and either pelvic or abdominal pain was complained of in 45 cases. Pain may be due to a twist of the tumor, which according to Graves is especially likely to occur in pregnancy, or to degeneration of the myoma, which Lynch<sup>11</sup> stated these tumors are markedly subject to during pregnancy. Although the majority of the patients suspected pregnancy because of one or more missed periods, seven consulted physicians complaining primarily of amenorrhea, and they did not suspect that they were pregnant. Hemorrhage is reported as the most common symptom in cases of uncomplicated fibroid tumors. However, in this study only seven patients complained of bleeding. In five cases hemorrhage occurred as menorrhagia (Table I).

TABLE I. PRESENTING COMPLAINT

Pregnancy; no previous diagnosis of myoma	21
Pregnancy without symptoms but previous diagnosis of myoma	12
Pregnancy with symptoms and with previous diagnosis of myoma	12
Tumor with pain; some, suspected pregnancy	20
Complaints without knowledge of pregnancy or myoma:	32
Amenorrhea	7
Pain in right lower quadrant	5
Pain in right upper quadrant	2
Abdominal cramps	1
Pain, pelvic	4
Suprapubic pain	2
Pain on defecation	1
Dysmenorrhea	1
Profuse menses	5
Intermenstrual bleeding	1
Vaginal discharge	1
Indigestion	2
Total	97

There is little doubt that uterine myomas play an important part in inducing miscarriage and premature labor, but various observers differ rather widely on the incidence of these conditions.

Roehrig reported 128 miscarriages out of 147 pregnancies; Giles, 95 out of 386. Campbell reported that 32 per cent of his patients had histories of "immature" births. Lockyer expressed the belief that the risk of abortion and premature labor is about 10 per cent. Lobenstine was able to show that in his series of 100 patients who had myomas, 85 per cent went to term.

All patients in this series had reached the period of viability of the fetus except those who underwent hysterectomy and most of those who underwent myomectomy. Of thirty-two patients on whom myomectomy was performed, twelve miscarried and three delivered prematurely. There were in addition three other premature deliveries.



Forty-six per cent of the entire group gave a history of one or more previous miscarriages. One patient had miscarried seven times.

One of us (Mussey) in 1922 stated that of 4,684 patients in whom hysterectomy was performed at the clinic, from 1910 to 1922, for benign uterine tumor, seven of the operations were performed on pregnant women. Since that time, in four additional cases hysterectomy has been performed on pregnant women.

Considerable discussion has arisen as to the correct management of pregnancy coexisting with uterine fibromyoma. In the paper just referred to it was stated that hysterectomy before the period of viability should be resorted to only when the patient has developed alarming symptoms. In three of these eleven cases in which hysterectomy was performed on pregnant uteri, there were symptoms of fetal death, and a macerated fetus was found in each case; in four cases hysterectomy was necessary because of evidence of degeneration in large myomas. In one case the uterus was removed because of uncontrollable bleeding; and in three cases, in which the patients were all more than forty years old and had large multiple myomas, pregnancy was not diagnosed prior to operation.

Cases in which there are symptoms of red degeneration present a particularly difficult problem as to whether or not myomectomy should be done. Lynch<sup>12</sup> was of the opinion that "one must have an exceptional case if operation is required," but that operation was indicated if pain from degeneration was not improved by rest. Polak stated that even with acute symptoms of necrobiosis it is safer to allow symptoms to subside than to attempt myomectomy. Goullioud reported three cases of rupture of the uterus during labor in a series of 100 cases in which myomectomy had previously been performed. W. J. Mayo has noted cases in which successful myomectomy has averted abortion. In our series of cases myomectomy was performed thirty-two times. The operation was thought advisable in twenty-one cases because of serious symptoms of degeneration or of necrosis, in seven because the tumor and pregnant uterus were impacted in the pelvic cavity, in three because of previous miscarriages, and in one because of threatened miscarriage (Table II).

In addition to fifteen cesarean sections, the conduct of labor was studied in fifty-nine cases, including one in which there was a set of twins, or a total of sixty deliveries by the vaginal route. Thirty-five of these patients, including thirteen who had undergone myomectomy, had spontaneous labors at term with no marked variation from the average duration of labor. Observers have reported that the position of the fetus was affected by the growth; Lynch<sup>13</sup> reported 22 per cent breech and 16 per cent shoulder presentations in cases in which this complication was present. In this series the presentation was breech in five cases and transverse in one; the remaining presentations were cephalic.

Premature rupture of the membranes has been estimated at as high as 75 per cent. In forty-four of Pierson's cases there was early rupture of the membranes; this was observed three times in this series.

TABLE II. OUTCOME OF PREGNANCY AFTER MYOMECTOMY

Primiparas:	
Miscarriages	5
Premature labor, 27 weeks, neonatal death	1
Normal, spontaneous deliveries at term	2
Low forceps deliveries at term	3
Breech, right sacral anterior, spontaneous delivery at term of stillborn, hydrocephalic fetus	1
Total	12
Multiparas:	
Miscarriages (1 maternal death, septicemia)	7
Normal, spontaneous deliveries at term	11
Premature, 30 weeks, spontaneous delivery of stillborn fetus	1
Premature, 33 weeks, spontaneous delivery of living child	1
Total	20

TABLE III. PREGNANCY COMPLICATED BY UTERINE MYOMAS  
PELVIC DELIVERY

60 labors		59 patients (one set of twins)	
Spontaneous deliveries at term			35
Following myomectomy		13	
Myomas not operated on		22	
Spontaneous premature deliveries			6
Following myomectomy		3	
Myomas not operated on		3	
Operative pelvic deliveries			19
Low forceps		10	
Persistent occipitoposterior position	2		
To hasten delivery (fetal asphyxia)	2		
Prophylactic forceps (maternal exhaustion)	3		
Uterine inertia	1		
Cardiac lesion	1		
Contraction of outlet	1		
Midforceps		2	
Deep transverse arrest	1		
Forceps rotation, occipitoposterior	1		
High forceps to engage head		1	
Breech extractions (4 mothers, twins once)		5	
Hysterostomy (Dührssen's cervical incision)		1	

Nauss estimated the occurrence of placenta previa as 2 per cent and LeFour as 4.2 per cent. One central placenta previa was observed in this series. Partial premature separation of the placenta occurred three times and abruptio placentae once. Retained placentas are said to be frequent complications; Scipidas estimated the Credé maneuver was used in 25 per cent of cases. Adherent placentas were encountered twice, necessitating manual removal. Postpartum hemorrhage occurred five times, requiring an intrauterine pack in each instance. Uterine inertia was observed once. There were no notable puerperal complications.

Among the sixty deliveries by the vaginal route there were nineteen operative deliveries, ten low forceps operations, three of which were done in cases in which myomectomy had been performed, two mid-

forceps operations, one high forceps operation, five breech extractions, and one Dührssen's incision of the cervix, an incidence of 31 per cent (Table III).

Cesarean section was performed fifteen times, in six cases the classical and in nine the Porro operation being employed. In twelve cases the tumor was a definite obstacle to delivery; one section was performed because of transverse presentation, one because of abruptio placentae, and one because of necrobiosis of the fibromyoma. There were no maternal deaths in this group (Table IV).

TABLE IV. PREGNANCY COMPLICATED BY UTERINE MYOMAS  
ABDOMINAL DELIVERY

INDICATIONS	CESAREAN SECTION		TOTAL
	CLASSICAL	PORRO	
Primiparas:			
Obstacle to delivery	3	2	5
Multiparas:			
Abruptio placentae		1	1
Transverse presentation		1	1
Obstacle to delivery	3	4	7
Myomatous degeneration		1	1
Total			15

Including breech extractions and abdominal deliveries, the obstetric operative deliveries in the seventy-four cases in which patients had attained the period of viability of the fetus, total 45 per cent; Campbell reported 46.2 per cent, Pierson 46 per cent, and Pinard 35 per cent. Eisaman reported a gross operative rate of 74.3 per cent and an abdominal delivery incidence of 56 per cent.

Until recently pregnancy in a myomatous uterus has been regarded as accompanied by grave risk to the mother.

LeFour reported a maternal mortality of 40 per cent in 300 vaginal deliveries and Bland reported eighty-seven versions with a maternal mortality of 64 per cent. Campbell reported three deaths in eighty-two cases. Pierson reported a 3.2 per cent mortality and Pinard 3.1 per cent. Landau reported a maternal mortality of 4.8 per cent in twenty-one cases in which myomectomy was performed. Troell estimated the maternal mortality following myomectomy at 4 per cent, and following cesarean section and myomectomy at 11.1 per cent. Kelly and Cullen had one maternal death in six cases in which myomectomy was performed. In this series of thirty-two cases in which myomectomy was done, there was one maternal death; the patient miscarried after the operation and died of a staphylococcic septicemia. One maternal death occurred after hysterectomy.

The fetal mortality is markedly increased when pregnancy occurs in myomatous uteri.

LeFour's fetal mortality was 77 per cent, whereas Bland reported 83 per cent. Pierson recently reported 35.6 per cent. Pinard gave a fetal mortality of 32.6 per cent and Campbell 25 per cent. Deducting the "immature" deaths from Campbell's statistics, the fetal mortality is 10 per cent. In our series eleven fetuses died in cases in which hysterectomy was performed, twelve died as a result of miscarriage

following myomectomy, three were stillborn (one was premature, one was a hydrocephalic monster, and one was a result of abruptio placentae) and two were premature and died shortly after birth; this gives a gross fetal mortality of 28.9 per cent and a fetal death rate of 6.6 per cent for the seventy-four cases in which the period of viability had been reached.

#### SUMMARY AND CONCLUSIONS

Of 297 cases in which pregnancy occurred in a myomatous uterus, there were ninety-seven, or a third, in which the situation, size, or symptoms produced by the myoma were of clinical significance. With the exception of those cases in which hysterectomy (eleven) or myomectomy (thirty-two) was performed early in pregnancy, in all cases in the series the period of viability of the fetus had been reached. Thus forty-three of the ninety-seven patients presented formidable complications comparatively early in pregnancy.

Fifteen, or 46 per cent, of the thirty-two patients who underwent myomectomy either miscarried or had premature labor. It is evident, then, that myomectomy during pregnancy carries with it a high fetal death rate and should not be done unless grave symptoms resulting from the myoma make operation imperative.

In those cases in which pregnancy proceeded to term, the combined obstetric and surgical operative incidence was 45 per cent. For the fifty-nine patients who were delivered by the pelvic route the operative obstetric procedures, not including breech extractions, were 23.7 per cent. Fetal mortality was extraordinarily high; 28.9 per cent for the ninety-seven cases in which the myomas were of clinical significance. This high fetal death rate is largely the result of hysterectomy performed early in pregnancy and the high incidence of miscarriages and premature labors following myomectomy. Of the seventy-five infants who reached the period of viability, five died, a fetal mortality of 6.6 per cent, in those patients who were delivered by the abdominal or pelvic route.

Pregnancy complicated by uterine fibromyomas is accompanied by increased but not unduly grave maternal risk. One death occurred in the group in which hysterectomy was done and one followed myomectomy, a total maternal death rate of 2 per cent. No maternal deaths occurred following cesarean section or vaginal delivery.

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## ON THE USE OF THE LUTEIN HORMONE, PROGESTIN, IN THREATENED AND HABITUAL ABORTION\*

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IN THE light of our present knowledge, it may be stated that the corpus luteum is the principal source of at least two hormones. It elaborates the lutein hormone, progesterin, in addition to producing even greater amounts of estrin than the graafian follicle. Adler, DeFrèmercy and Tausk<sup>1</sup> have isolated progesterin from the placenta using a method for the quantitative separation of estrin and progesterin recently described by Allen and Meyer.<sup>2</sup> It is not definitely known whether the placenta actually produces this hormone or merely stores it.

The physiologic effects of the luteal hormone on the genital tract have been studied by numerous investigators and certain definite facts are now accepted as a result of their experimentation. Weichert,<sup>3</sup> Corner and Allen,<sup>4</sup> and others,<sup>5</sup> have demonstrated that subsequent to the preliminary influence of estrin, progesterin prepares the endometrium for the reception and nourishment of the fertilized ovum. Hisaw<sup>6</sup> first showed the inhibitory effect of progesterin on uterine contractions and Morrell<sup>7</sup> (quoted by Mazer and Goldstein), illustrated its ability to nullify the effect of pituitrin. Corner and Allen<sup>8</sup> conclusively proved that the lutein hormone is essential for the conservation of early pregnancy, and Miklós<sup>9</sup> noted that progesterin, when present in excessive amounts, was able to prolong gestation. The inhibition of ovulation as shown by Papanicolaou,<sup>10</sup> Macht,<sup>11</sup> and Imperato,<sup>12</sup> and the maintenance of estrin balance by promoting excretion of this substance by the kidney (Smith and Smith<sup>13</sup>) are additional important functions of the corpus luteum hormone. It has not as yet been positively determined whether the changes produced in the endometrium and the inhibition of the oxytocic action of pituitrin are the result of the activity of one or separate luteal hormones.

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The intimate interrelationship between the corpus luteum and the fertilized ovum during early pregnancy has long been established. In 1903, Fraenkel<sup>14</sup> demonstrated that the removal of the corpus luteum of early pregnancy resulted in absorption or premature expulsion of the fetus of a rabbit. Conversely, the interruption of gestation results in regression of the corpus luteum. The experiments of Knaus<sup>15</sup> and Manzi<sup>16</sup> show that the administration of progestin maintains the uterus in a state of quiescence during pregnancy, rendering it insensitive to pituitrin. This may explain why pituitrin fails to produce abortion in the early months of gestation, whereas it is capable of terminating pregnancy in its later stages. Excessive doses of the follicular hormone have been shown to produce abortion in animals by Parkes,<sup>17</sup> Kelly,<sup>18</sup> and Zondek and Aschheim.<sup>19</sup> Brouha and Simonnet<sup>20</sup> proved that injections of estrin sensitized the uterus to the action of pituitrin. Progestin and estrin appear, therefore, to be antagonistic in their effects on uterine contractions.

These facts have led to the development of the theory that pregnancy continues while the corpus luteum is in the ascendancy, but if estrin becomes dominant, the uterus is sensitized to pituitrin and labor ensues. Jeffcoate,<sup>21</sup> in doing Aschheim-Zondek tests for pregnancy, noted on a few occasions a modified reaction which he attributed to a relative excess of estrin in the urine over Prolans A and B. The patients whose urine gave this modified reaction, almost invariably aborted or passed a macerated fetus soon afterward.

It is not our purpose to go into a detailed discussion of the various types of abortion of known etiology. We are particularly concerned with that group of spontaneous abortions occurring without recognizable cause. The majority of these cases are probably the result of an hormonal disturbance. Our conception of the etiology of abortion in this group of patients is that there is a deficiency of the corpus luteum hormone, either relative or absolute, which may manifest itself in several ways:

1. By an excess and overactivity of estrin due to diminished excretion which sensitizes the uterus to the action of pituitrin, thus initiating contractions.

2. By inadequate decidual reaction which may result in (a) undernourishment and death of the fertilized ovum after implantation with automatic expulsion or absorption; (b) deficient placentation which in turn may cause a deficiency of progestin in the placenta.

3. By increasing the hemorrhagic tendency in the uterine endometrium produce premature detachment of the placenta in certain cases. (It is claimed by Seitz, Wintz and Fingerhut<sup>22</sup> that corpus luteum extract shortens the coagulation time of the blood.)

If this conception is correct, it is logical to treat cases of threatened and habitual abortion with the corpus luteum hormone.

In 1913, Seitz<sup>23</sup> suggested careful observation of the corpus luteum for pathologic changes whenever possible in cases of habitual abortion. Attempts to treat habitual abortion with corpus luteum extract date back as far as 1919, when Hirst<sup>24</sup> employed injections of the aqueous extract of corpora lutea obtained from pregnant cattle. Hannes,<sup>25</sup> in the same year, suggested that such an extract might be useful in the treatment of spontaneous abortion. In 1920, Hofbauer<sup>26</sup> noted an inhibition of uterine contractions in threatened and habitual abortion following the use of a preparation called "ovoglandol." The following year, J. Halban<sup>27</sup> advised the use of corpus luteum extract in abortion. Glismann,<sup>28</sup> in 1928, reported the successful use of "lipo-lutin" in the treatment of recurrent abortion. The products used by these

investigators were not standardized and probably contained relatively small amounts of the nidatory principle. Nevertheless, their results were encouraging.

More recently, Anteck and Zwolinski<sup>29</sup> reported twenty-one cases of habitual abortion of which nineteen went to term with daily treatment with "lutophorin," a corpus luteum preparation. H. Wolfsohn<sup>30</sup> used "luteogan" with success in seven of ten cases of habitual abortion. He attributed one of the three failures to a fibroid uterus and another to an hydatid mole. Weinzierl<sup>31</sup> reported a series of six cases of habitual abortion favorably treated with the lutein hormone. Bracht<sup>32</sup> successfully employed the corpus luteum hormone in the treatment of four cases of habitual abortion. Wagner<sup>33</sup> and Knab<sup>34</sup> mention that they have used the corpus luteum hormone with success in several cases of habitual abortion. Isolated case reports by Lopez-Doriga,<sup>35</sup> Lind,<sup>36</sup> Patti,<sup>37</sup> and Shea<sup>38</sup> of successful treatment using various preparations of the corpus luteum in threatened and habitual abortion have been made.

Sellheim<sup>39</sup> used the blood serum of normal pregnant females in the treatment of five cases of habitual abortion and two cases of threatened abortion. He believes that the substance which prevented abortion in these patients was the corpus luteum hormone present in the blood of these normal pregnant women.

Witherspoon<sup>40</sup> administered the anterior pituitary luteinizing hormone in cases of threatened abortion with the hope of stimulating the corpus luteum of pregnancy to increased production of progesterin. Theoretically, there is the objection that it may simultaneously increase the production of estrin which might have the effect of stimulating uterine contractions. His results are unconvincing in that abortion was prevented in only 6 or 50 per cent of the cases while in the hospital. Four of these patients aborted within a week following their discharge from the hospital after all injections of the anterior pituitary luteinizing hormone had been discontinued\*

#### METHOD OF PREPARATION

The corpora lutea are carefully dissected from freshly frozen hog ovaries, very finely ground, and extracted with three parts of 95 per cent alcohol. The alcoholic extract is removed by pressing and the residue is extracted with three successive portions of 95 per cent alcohol. The alcoholic extracts are combined and concentrated in vacuo until all alcohol is removed. The resulting aqueous concentrate is thoroughly extracted with ethyl acetate, the ethyl acetate solution treated with a 10 per cent solution of sodium carbonate and followed by thorough washing with water. The ethyl acetate solution is evaporated to dryness in vacuo at a low temperature and the residue dissolved in alcohol. The alcoholic solution is diluted with water to a concentration of 70 per cent alcohol. After cooling to zero, the 70 per cent alcohol solution is filtered and concentrated in vacuo until all alcohol is removed. The aqueous concentrate is extracted with benzene, the benzene solution evaporated to dryness and the residue dissolved in a highly purified animal oil. This oil solution is assayed by injecting into rabbits and is then diluted to contain the required rabbit unitage. It is then filtered through a sterilized Berkefeld or Seitz filter and filled into sterile ampules.

#### PHYSIOLOGIC ASSAY

The test is based on the production of progestational proliferation in the uterine mucosa of castrated rabbits by injections of corpus luteum extracts.

Mature does, isolated for three weeks or more, are anesthetized with ether, and the ovaries with small portions of the fallopian tubes are removed under aseptic condi-

\*NOTE: The corpus luteum hormone which we used in the treatment of our patients was prepared and assayed in the Reed and Carnrick Laboratories, Jersey City, N. J., to whom we wish to express our appreciation.

tions. A piece of the uterus, usually from the middle of the left horn, is removed at the same time as a histologic control (Fig. 1). The spayed rabbits are divided into groups and the corpus luteum extract is tested at two or more dosages. The extract is injected subcutaneously on the lateral surface of the body in equal doses,

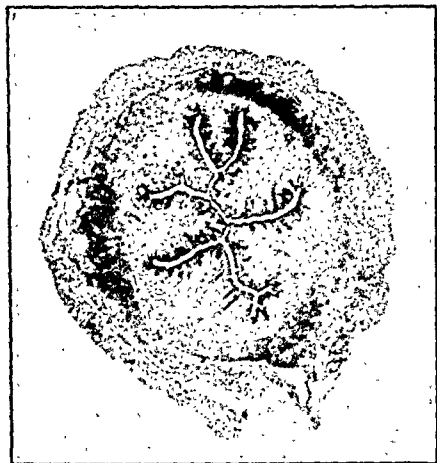


Fig. 1.

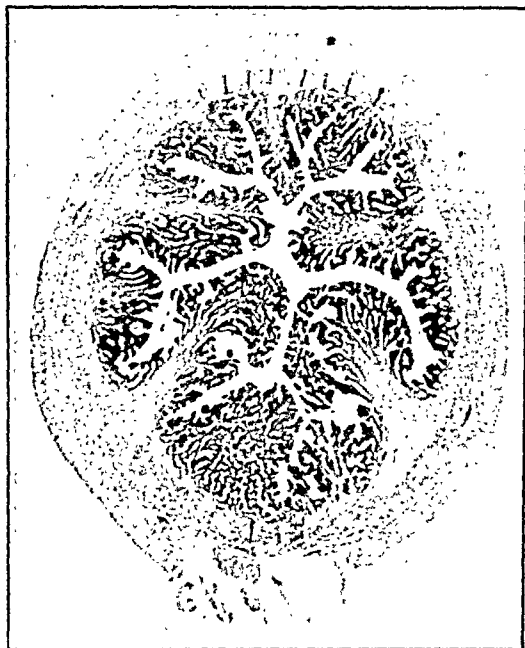


Fig. 2.

Fig. 1.—Control tissue. Section from horn of uterus of mature doe.  $\times 10$ .

Fig. 2.—Section from horn of uterus of spayed rabbit following injection of corpus luteum hormone.  $\times 10$ .

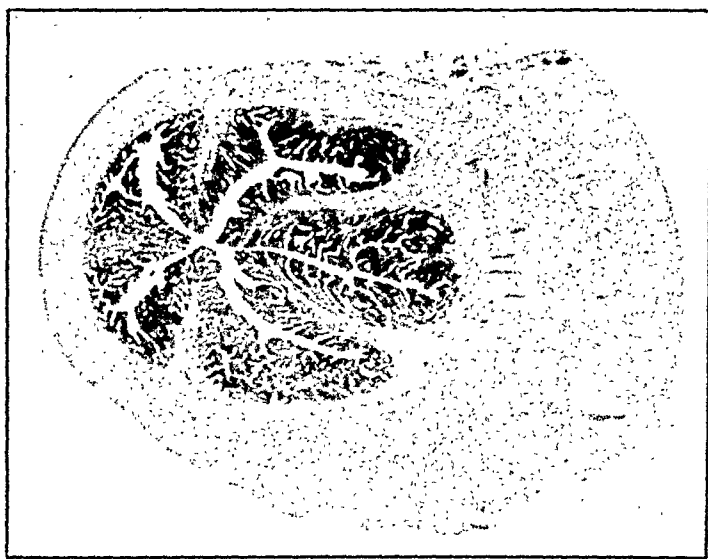


Fig. 3.—Section from horn of rabbit uterus of standard eight-day pregnancy.  $\times 10$ .

once daily for five days, the first dose being injected soon after the operation. The rabbits are killed twenty-four hours after the last injection. The condition, size, and color of each uterus are noted and portions of each horn are preserved in Bonin's fluid for sectioning.



TABLE I

CASE NO.	Name	Age	Race	Para	Gravida	MENSTRUAL HISTORY	LAST MENSTRUAL PERIOD	PREVIOUS ABORTIONS OR MISCARRIAGES	ASSOCIATED PATHOLOGY
1	H. C.	29	W	III	VII	Normal	11/15/33 (?)	IV Spontaneous abortion at 3-4 mo. V Spontaneous abortion at 3-4 mo. VI Spontaneous abortion at 3-4 mo.	Right Salpingo-oophoritis.
2	P. S.	27	W	I	V	Regular but scant. Pain first day.	11/27/33 (?)	I Spontaneous abortion at 6 wks. II Spontaneous abortion at 6 wks. III Premature labor at 7 mo. Child L. & W. IV Miscarriage at 6 mo.	None
3	R. W.	31	W	II	III	Regular but profuse. Pain 1st. 2 days.	12/16/33	I Premature labor at 8 mo. Child died 2 wks. later. Cause?	None
4	T. Y.	21	C	O	I	Normal	12/26/33	None	Rheumatic heart disease.
5	H. C.	27	W	O	VII	Normal	12/31/33	I Spontaneous abortion at 2 ½ mo. II Spontaneous abortion at 2 ½ mo. III Spontaneous abortion at 2 ½ mo. IV Spontaneous abortion at 2 ½ mo. V Spontaneous abortion at 2 ½ mo. VI Spontaneous abortion at 2 ½ mo.	None
6	E. T.	33	W	I	VI	Normal	1/10/34	II Spontaneous abortion at 3 ½ mo. III Spontaneous abortion at 2 ½ mo. IV Spontaneous abortion at 2 ½ mo. V Spontaneous abortion at 2 ½ mo.	None
7	E. P.	20	W	O	II	Regular but profuse.	2/13/34	I Spontaneous miscarriage at 6 mo.	Rheumatic heart disease.
8	A. L.	26	W	O	III	Normal	3/5/34	I Spontaneous twin miscarriage at 6 mo. II Spontaneous twin miscarriage at 6 mo.	Bicornuate uterus.
9	P. R.	28	W	O	III	Normal	3/10/34	I Spontaneous abortion at 2 mo. II Spontaneous abortion at 2 mo.	None
10	E. D.	31	W	II	V	Severe pain 1 wk. before onset.	3/15/34	I Spontaneous abortion at 3 mo. IV Spontaneous abortion at 3 mo.	None
11	H. L.	28	W	O	II	Normal	4/22/34	I Spontaneous abortion at 6 wks.	None
12	M. T.	20	W	O	II	Irregular Usually 2-3 wks. late.	5/1/34	I Spontaneous abortion at 3 mo.	None
13	H. T.	25	W	O	IV	Normal	5/2/34	I Spontaneous abortion at 3 mo. II Spontaneous abortion at 3 mo. III Spontaneous abortion at 3 mo.	None
14	H. C.	33	W	II	IV	Normal	5/11/34	II Spontaneous abortion at 2 ½ mo.	Twin pregnancy.
15	P. C.	30	W	O	I	Normal	5/28/34	None	None
16	N. F.	24	W	O	III	Normal	6/8/34 (?)	I Spontaneous abortion at 2 mo. II Spontaneous abortion at 2 mo.	None
17	D. F.	29	W	II	III	Profuse	6/8/34	None	3rd° retroversion corrected.
18	A. C.	25	W	O	III	Severe cramps and headache for 1st 3 days.	6/22/34	I Spontaneous abortion at 2 ½ mo. II Criminal abortion at 2 mo.	None
19	R. D.	20	C	O	III	Normal	6/27/34	I Spontaneous abortion at 6 wks. II Spontaneous abortion at 6 wks.	None

TABLE I—Cont'd

Wassermann	PRESENT COMPLAINT	EXAMINATION	DIAGNOSIS	PROGRESS	RESULT
Neg.	Lower abdominal pains. Backache.	Uterus size of 4½-5 mo. pregnancy 4/12/34	Threatened and habitual abortion.	Pains subsided following progestin therapy. Normal spontaneous full-term delivery.	Success
Neg.	None. Spotted and had cramps at 6 wks.	Uterus size of 5 mo. pregnancy 3/28/34	Habitual abortion.	Uneventful. Normal spontaneous full-term delivery. 8/1/34	Success
Neg.	Abdominal pains and bleeding for 1 mo.	Uterus size of 6 mo. pregnancy. Blood escaping from cervical canal 5/2/34	Threatened miscarriage.	Bleeding and pains gradually subsided. No complaints after 2 wks. Normal spontaneous full-term delivery. 9/3/34	Success
Neg.	Lower abdominal pains at 5 min. intervals.	Uterus size of 6 mo. pregnancy. Contracted pelvis. 6/6/34	Threatened miscarriage.	Pains subsided following progestin therapy. Progress uneventful. Cesarean section 10/3/34. Normal full-term baby	Success
Neg.	Spotting for 1 mo.	Uterus size of 4 mo. pregnancy 4/25/34	Threatened and habitual abortion	Bag of waters ruptured 8/19/34. No pains. Spontaneous 7½ mo. premature. 8/21/34. Baby died 12 hrs. later. Autopsy revealed pulmonary atelectasis.	Failure
Neg.	None	Uterus dextro-deviated. Size of 2-2½ mo. pregnancy 3/15/34	Habitual abortion.	Uneventful. Normal spontaneous full-term delivery. 10/6/34	Success
Neg.	None	Uterus size of 3½ mo. pregnancy 5/16/34	Habitual abortion.	Threatened to abort at 4 mo. Polyhydramnios. 6½ mo. miscarriage 9/6/34.	Failure
Neg.	Occasional lower abdominal pains.	Uterus size of 5 mo. pregnancy	Habitual abortion.	Uneventful. No pains since progestin therapy.	Success
Neg.	None	Uterus size of 6 wk. pregnancy 4/1/34	Habitual abortion.	Uneventful	Success
Neg.	None	Uterus size of 7 wk. pregnancy 4/30/34	Habitual abortion.	Spontaneous abortion at 3 mo. 6/17/34	Failure
Neg.	Abdominal cramps and spotting.	Uterus size of 6 wk. pregnancy 6/11/34	Threatened and habitual abortion.	Symptoms subsided in 1 wk. Pains recurred on Aug. 4. Subsided. Progress uneventful.	Success
Neg.	Abdominal cramps and slight bleeding for 36 hrs.	Uterus size of 3 mo. pregnancy 6/13/34	Threatened and habitual abortion.	Symptoms subsided in 1 day. Progress uneventful.	Success
Neg.	None	Uterus size of 4 mo. pregnancy 9/15/34	Habitual abortion.	Uneventful	Success
Neg.	Lower abdominal cramps and slight bleeding.	Uterus size of 3 mo. pregnancy 7/29/34	Threatened abortion.	Cramps subsided in 1 day. Bleeding subsided in 3 days. Progress uneventful.	Success
Neg.	Bleeding - 2 days. Had bleeding on 8/25/34 for 1 day.	Uterus size of 3½ mo. pregnancy 9/6/34	Threatened abortion.	Bleeding subsided following progestin therapy.	Success
Neg.	None	Uterus size of 2 mo. pregnancy 9/8/34	Habitual abortion.	Spontaneous abortion at 3 mo.	Failure
Neg.	Cramps and profuse bleeding 1 mo.	Uterus size of 3½ mo. pregnancy 8/10/34	Threatened abortion.	Bleeding subsided after 5 days of progestin therapy. Recurred 3 days later. Spontaneous abortion 8/22/34.	Failure
Neg.	Lower abdominal cramps and bleeding.	Uterus size of 3 mo. pregnancy 9/15/34	Threatened and habitual abortion.	Symptoms subsided after 4 days of progestin therapy. Progress uneventful.	Success
Neg.	Profuse bleeding.	Uterus size of 4 mo. pregnancy 10/5/34	Threatened and habitual abortion.	Bleeding subsided after 4 days of progestin therapy. Progress uneventful.	Success

The mounted sections (Fig. 2), stained with hemotoxylin and eosin, are compared with the controls and with the standards (eight-day pregnancy) (Fig. 3) to determine the degree of proliferation obtained with the extract.

If a proliferation equal to an average eight-day pregnancy is obtained with one of the doses, injected in five equal portions, this dose contains one rabbit unit.

In general, this procedure follows that of Corner and Allen,<sup>4</sup> except that the mature does are not mated previous to spaying.

In order to obtain fairly accurate quantitative results, at least five carefully selected rabbits must be used for each dosage.

#### PERSONAL OBSERVATIONS

A series of nineteen patients with threatened and habitual abortions were treated with the lutein hormone. In the group of habitual abortions, all patients who gave a history of one or more spontaneous abortions were included. Those patients who had persistent regular, painful uterine contractions or in whom there was a loss of blood from the uterus sufficient to be termed a true bleeding and not a slight spotting were considered threatened abortions. In some cases, both of these symptoms were present. Some of the patients with threatened abortion also belonged to the group of habitual abortion.

Patients in this series were from various social levels. They were about equally divided between private and dispensary patients. The latter group, in spite of the demands of their daily routine, were equally responsive to the treatment.

One cubic centimeter ampules containing one rabbit unit of the lutein hormone were injected intramuscularly. The following definite predetermined routine was followed as closely as possible. The patients with a history of habitual abortion but without symptoms, received prophylactic injections of one rabbit unit twice weekly until the thirty-second week of gestation and were permitted to be ambulatory. Patients who presented themselves with symptoms of threatened abortion were confined to bed either in the hospital or at home and received one rabbit unit of the corpus luteum hormone twice daily until all symptoms subsided. One rabbit unit was then administered daily for the following week. If the patients remained symptom-free, they received one rabbit unit twice weekly until the thirty-second week. No attempt was made to treat a patient who had ruptured membranes or a negative pregnancy test.

#### RESULTS

A total of 19 patients received progestin therapy (see Table I). Of these, 14 or approximately 74 per cent were considered successful in that they either went to term or all symptoms of threatened abortion subsided with an uneventful progress up to the present time. One of the five cases classified as failures was not an absolute failure as far as progestin therapy was concerned. She belonged to the group of threatened and habitual abortion and had previously aborted six times at two and a half months. Her progress was uneventful up to seven and a half months, at which time the membranes ruptured and labor ensued two days later. The fetus was viable but died twelve hours after delivery as the result of a pulmonary atelectasis which was demonstrated at autopsy. One other patient, who previously had a spontaneous miscarriage at six months, developed a polyhydramnios and went into premature labor at six and a half months.

Eleven of the total number of cases were classified as threatened abortions. Nine patients or 82 per cent were treated successfully and two or 18 per cent were failures. Six of the patients with threatened abortions had a history of previous spontaneous abortions. Eight patients with a history of habitual abortion were treated prophylactically. Five or 62.5 per cent were successful and three or 37.5 per cent were failures.

It is interesting to note that this group of 19 patients had a total of 48 previous pregnancies before progestin therapy was used. Only 15 or 31 per cent of the previous pregnancies went to term and the remaining 33 or 69 per cent terminated in abortion.

#### DISCUSSION

The dosage of the hormone used, one rabbit unit, was empirical, and we are unable to state as yet whether a stronger or less potent preparation is necessary to obtain the optimum effect. Work on this point is in progress. It is probable that the amount necessary to produce the most desirable result will vary in different individuals, depending on the amount of deficiency of the corpus luteum hormone.

Because it is difficult clinically to detect the death of the fetus in a case of threatened abortion, in some of the cases in which failure occurred, the fetus may have been dead at the time treatment was instituted. The fact that the Aschheim-Zondek test and its modifications are frequently positive in such cases for a variable length of time, renders this test unreliable under these circumstances. The urine pregnancy test is only of value in these cases when the reaction is negative. The Frank-Goldberger method for the female sex hormone determination in the blood is said to give reliable information as to the life or death of the fetus.<sup>41</sup> We would advocate, therefore, treating all cases of threatened abortion with progestin until a negative female sex hormone reaction is obtained.

Sedatives were purposely omitted in the treatment of these patients to avoid confusion concerning the results obtained.

Progestin appears to be just as effective in threatened miscarriages as in threatened abortion.

#### CONCLUSIONS

1. The cause of a large number of spontaneous abortions and miscarriages is a deficiency of the corpus luteum hormone.
2. Substitutional therapy with the lutein hormone to overcome this deficiency is logical and valuable.
3. Prophylactic treatment with this hormone should be administered to patients with a history of habitual abortion before signs of threatened abortion appear.
4. Patients with threatened abortion should be treated actively with progestin and the therapy should not be discontinued until the death of the fetus has been definitely established.

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Sodano determined the ratio between the amount of agglutinins in the maternal blood serum and the milk by their reaction to the colon bacillus. He found that during the first week of the puerperium the amount in the milk closely approached the amount in the blood serum.

He then vaccinated women with various dilutions of *B. coli* during the last few weeks of gestation in order to build up their resistance to the organisms. During the first week of the puerperium, however, the amount of agglutinins in their milk was always very much less than in the blood serum.

It would seem then that the building up of antibodies in the maternal blood serum does not increase the amount in the milk fed the child.

JAMES M. PIERCE.

# A STUDY OF NEMBUTAL AND SCOPOLAMINE FOR THE RELIEF OF PAIN IN FIVE HUNDRED DELIVERIES\*

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AT THE Evanston Hospital during the past two years we have used nembutal and scopolamine for the relief of pain in the majority of the obstetric cases. During the time that these 500 cases used in this study were accumulating, we delivered 783 patients which means that we administered these drugs to 63.8 per cent. Two hundred and seventy-five were primiparas and 225 were multiparas. The two groups will be reported separately and then some of the totals will be given.

TABLE I. PRIMIPARAS, TYPE OF DELIVERY

Low forceps	191
Manual rotation and low forceps	18
Manual rotation and midforceps	5
Cesarean section	2
Version and forceps	2
Version without forceps	1
Breech with forceps	7
Breech without forceps	4
Midforceps	4
High forceps	1
Spontaneous	40
Total	275
Operative incidence	85%

## METHOD

The primiparas received an average of 9.03 gr. of nembutal in an average of 1.97 doses together with  $\frac{1}{150}$  gr. of scopolamine. The nembutal was given by mouth and the scopolamine hypodermically. The first dose of nembutal was generally  $7\frac{1}{2}$  gr. and the scopolamine was given at the same time that the nembutal was administered. Later on, as the patient needed it, additional nembutal was given in 1.5 or 3 gr. doses from one and one-half to three hours apart or even longer. The largest amount of nembutal given to any patient was 22.5 gr. over a period of thirty-seven hours. The last dose was given to this patient two hours and twenty minutes before delivery and she was awake thirty-seven minutes after being delivered. She received very little benefit from the drug and reported that she thought she had had a hard labor. The average time from the first dose to delivery in the primipara was four hours and forty minutes. The average duration of labor was twelve hours and thirty-nine minutes.

\*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.

At the time of delivery 254 of these 275 primiparas received gas for complete anesthesia. Ethylene was used in the large majority, a moderate number were given nitrous oxide and in a few cases in which version, breech extraction, or manual rotation was done, drop ether was used.

The pulse and blood pressure were taken on entrance, one hour after the drugs were administered, just before delivery and shortly after delivery. The amount of bleeding was also noted. These are found in Table II.

TABLE II. PRIMIPARAS

Blood Pressure:	
Below 100	27 cases
Above 140	35 cases
Pulse:	
Below 70	90 cases
Above 110	24 cases
Increased Bleeding:	
Cases	20
Average amount	462 c.c.

There were two cases of shock—one a case of twins and the other following a difficult delivery where the baby weighed nine pounds thirteen ounces. The period of shock in both cases was of short duration. The majority of the cases of increased bleeding were not severe. The uterus was packed only five times. Intravenous solutions were given four times and transfusion was used only twice.

The average elapsed time between delivery and the time at which the patient was considered awake and rational was five hours and twenty-one minutes. The period that elapsed between the first dose and awakening averaged ten hours and eight minutes. The period that elapsed between the last dose of nembutal and awakening averaged eight hours and three minutes.

TABLE III. PRIMIPARAS

Average duration of sleep after first dose of nembutal	10 hr. 8 min.
Average duration of sleep after last dose of nembutal	8 hr. 3 min.
Average duration of sleep after delivery	5 hr. 21 min.

TABLE IV. PRIMIPARAS

Of 235 cases reporting:	
Memory clear after first dose	26
Memory clear after second dose	9
Memory clear after third dose	3
Memory clear after fourth dose	1
Memory vague after first dose	70
Memory vague after second dose	20
Memory vague after third dose	3
Memory vague after fourth dose	0
Remember nothing after first dose	127
Remember nothing after second dose	20
Remember nothing after third dose	3
Remember nothing after fourth dose	0

About the third day after delivery most of the patients were interviewed by the house physicians and asked to tell what they could remember about their labors and what their opinions were as to the results. The information obtained is given in Tables IV and V.

The condition of all babies at birth was charted and from these charts was obtained the information found in Table VI. Only the findings other than normal are noted.

TABLE V. PRIMIPARAS

Patient thought she had an easy time	143
Patient thought she had a moderately easy time	40
Patient thought she had a moderately hard time	24
Patient thought she had a hard time	5
Total number reporting	212

Among the 275 primiparas there were three fetal deaths, two of which could be classed as obstetric deaths. The other was a case of meningoencephalocoele.

TABLE VI. PRIMIPARAS, CONDITION OF BABY

Color:	
Blue	31
Pallid	9
Mucus:	
Increased amount	32
Less than usual	16
Medication:	
Total cases receiving	19
Lobelin	1
Coramine	18
Adrenalin	2
Intramuscular injections of whole blood	21
Resuscitation:	
Water-bath	21
CO <sub>2</sub> + O	26
Aspiration	12
Artificial respiration	1

TABLE VII. PRIMIPARAS, BABIES DISCHARGED WITH MOTHER

Yes (one set of twins)	267
No	9
Stillbirths	2
Premature (lived)	4
Cerebral injury (death)	1
Impetigo (lived)	1
Harelip (lived)	1

Information concerning the two obstetric deaths is given in Table VIII.

There was one maternal death. She was a primipara, aged thirty-six, who died of hemorrhage a few hours after a cesarean section. She was fully conscious when taken to the operating room and had been for about eight hours. Autopsy revealed nothing but large open veins at the placental site. She had been in labor over thirty hours without progress.

Tables IX to XVI inclusive give the same information about the multiparas that has been given in the preceding tables concerning the primiparas. There were 225 multiparas.

The average duration of labor for the multipara was eight hours. The average total dose of nembutal was 8.07 gr. given in 1.5 doses. The time of administering the initial dose was two hours and thirty-four minutes before delivery. All patients were given scopolamine  $\frac{1}{150}$  gr. by hypodermic at the same time that the first dose of nembutal was given. At the time of delivery 212 were given gas for complete anesthesia.



TABLE VIII. PRIMIPARAS, FETAL DEATHS

No. 1. Weight 8 pounds 2½ ounces. Difficult labor, 16 hours. Second stage 5½ hr.	
Mother received:	
1:45 A.M.	Nembutal gr. 6 and scopolamine gr. ¼ <sub>150</sub>
3:00 A.M.	Nembutal gr. 1½
7:30 A.M.	Nembutal gr. 1½
2:35 P.M.	Thymophysin M. iii
3:40 P.M.	Had a large brown emesis during the anesthetic, became cyanotic; CO <sub>2</sub> +O given
3:54 P.M.	Babe delivered.
	Difficult resuscitation; respirations shallow, rapid, irregular; abdominal type of breathing; spastic.
	Clinical diagnosis: Cerebral hemorrhage (severe).
	Died in 35 hours.
	Postmortem diagnosis: Asphyxia neonatorum. No hemorrhage found.
No. 2. Stillbirth. Twelve-hour labor; baby large; pelvis small; very hard mid-forceps delivery; much difficulty with shoulders.	
Weight 9 pounds 12¾ ounces.	
Postmortem diagnosis: Laceration of tentorium; pulmonary atelectasis.	
Mother received:	
3:15 A.M.	Nembutal gr. 7½ and scopolamine gr. ¼ <sub>150</sub>
4:50 A.M.	Nembutal gr. 1½
6:40 A.M.	Thymophysin M. iii
11:40 A.M.	Babe delivered.

TABLE IX. MULTIPARAS, TYPE OF DELIVERY

Cesarean section	1
Manual rotation with low forceps	4
Manual rotation with midforceps	0
Version with forceps	1
Version without forceps	3
Breech with forceps	4
Breech without forceps	3
Low forceps	92
Spontaneous	119
Total (two sets of twins)	227
Operative incidence	48%

TABLE X. MULTIPARAS

Blood Pressure:	
Above 140	21
Below 100	14
Pulse:	
Above 110	4
Below 70	53
Bleeding Increased:	
Cases	15
Average amount lost	497
Intravenous given	2
Intramuscular injection of whole blood	0

There were no cases of shock and the uterus was packed only twice showing that the average blood loss was only moderately increased.

TABLE XI. MULTIPARAS

Average duration of sleep after first dose of nembutal	8 hr. 1 min.
Average duration of sleep after last dose of nembutal	7 hr. 12 min.
Average duration of sleep after delivery	5 hr. 31 min.

TABLE XII. MULTIPARAS

Of 183 cases reported:	
Memory clear after first dose	23
Memory clear after second dose	2
Memory clear after third dose	0
Memory clear after fourth dose	0
Memory vague after first dose	62
Memory vague after second dose	2
Memory vague after third dose	2
Memory vague after fourth dose	1
Remember nothing after first dose	97
Remember nothing after second dose	16
Remember nothing after third dose	0
Remember nothing after fourth dose	0

TABLE XIII. MULTIPARAS

Of 171 cases reported:	
Patient thought she had an easy time	130
Patient thought she had a moderately easy time	24
Patient thought she had a moderately hard time	13
Patient thought she had a hard time	3
Patient thought she had a very hard time	1

TABLE XIV. MULTIPARAS, CONDITION OF BABY AT BIRTH

Color:	
Blue	22
Pallid	0
Mucus:	
Increased amount	11
Less	25
Medication:	
Total cases receiving (Coramine used in all)	5
Resuscitation:	
Water-bath	5
CO <sub>2</sub> + O	5
Aspiration	2

There was only one fetal death among the multiparas. There were no maternal deaths.

The stillbirth followed a low cervical section. No engagement after twenty-four hours of labor; generally contracted pelvis.

Mother received:

12:30 P.M. Nembutal gr.  $7\frac{1}{2}$  and scopolamine gr.  $\frac{1}{150}$   
 1:30 P.M. Nembutal gr.  $1\frac{1}{2}$  (Vomited immediately)  
 2:00 P.M. Nembutal gr.  $1\frac{1}{2}$   
 4:00 P.M. Nembutal gr.  $1\frac{1}{2}$   
 7:30 P.M. Nembutal gr.  $1\frac{1}{2}$   
 9:35 P.M. Morphine sulphate gr.  $\frac{1}{4}$   
 7:20 A.M. Atrophine sulphate gr.  $\frac{1}{150}$  } Preop. for section  
 8:10 A.M. Morphine sulphate gr.  $\frac{1}{6}$  }  
 From 4:30 to 9:30 P.M. 16 oz. ether given with pains by inhalation.  
 6:00 A.M. Babe delivered. Weight, 7 pounds 14 ounces.

Postmortem anatomic diagnosis: High-grade passive hyperemia and edema of brain. Ecchymotic hemorrhages of the thymus, pericardium and pleura. Cyanosis

TABLE XV. MULTIPARAS, BABIES

Discharged with mother	221
Not discharged with mother	6
Stillbirth	1
Premature (lived)	3
Cerebral injury (lived)	1
Remained as boarder	1

of all of the thoracic and abdominal organs and of the skin of the surface of the body. Chief diagnosis: Asphyxia neonatorum.

Further information concerning the condition of the babies was compiled by means of charts, using 75 unselected cases. The type of delivery in these cases was as follows: spontaneous 20, low forceps 47, midforceps 1, version 3, and breech extraction 4. The color at birth was classified as good in 47 cases, fair in 26, and poor in 2. Nine of these 75 needed some form of resuscitation. Coramine was used in three, lobeline in one and the other five were given a hot bath and a mixture of carbon dioxide and oxygen. The pulse and respiration rates were noted at birth and after twelve, twenty-four, and forty-eight hours, respectively. The information is set forth in Table XVI.

The moro reflex, the deep tendon reflex and the response to foot pressure were all noted at the same stated intervals as were respiration and pulse and the findings are set forth in Table XVII.

TABLE XVI

	PULSE AVERAGES	RESPIRATION AVERAGES
Birth	117	50
12 Hours	119	46
24 Hours	123	48
48 Hours	126	49

TABLE XVII

	MORO			DEEP TENDON			FOOT PRESSURE		
	ABSENT	POOR	NORMAL	ABSENT	POOR	NORMAL	ABSENT	POOR	NORMAL
Birth	13	27	25	4	48	18	3	42	25
12 Hr.	5	31	14	0	48	19	2	39	18
24 Hr.	2	47	17	0	46	12	1	29	28
48 Hr.	1	18	36	0	36	22	0	22	35

It will be noted that the totals for each period do not reach 75, but we feel sure that sufficient information is given to show the general trend. All of these 75 babies left the hospital in good condition.

Members of the patients' families were interviewed as to their opinion of the drugs, and their replies showed approval of the procedure in 94 out of 97 primiparas that were reached and 84 out of 99 multiparas. The 18 relatives registering complaints were predominantly from the group of multiparas for it was in this group that the largest number of failures occurred.

Out of the 500 cases here reported there were 32 cases in which the drugs failed to give relief of pain and to cause loss of memory. Among these 22 cases were patients who vomited all or part of the medication, and others, especially multiparas, who received it too late. Thus the drugs were successful in 93.6 per cent. Among the failures were 7 patients weighing between 160 and 210 pounds. The average primipara in this series weighed 136 pounds and the average multipara 141 pounds.

The majority of these patients were restless during pains especially during the last part of the first stage and the second stage of labor. This restlessness, however, does not seem to be of any importance, providing the patient receives proper and constant nursing care. We have insisted that each patient have a nurse from the time she receives the first dose until after she is awake and rational. From the data presented here, that means from ten to twenty-four hours.

There are, however, a few patients who become stimulated or irritated by the drugs and who show some violence whether they are having a pain or not. There were twelve of these in this series, ten primiparas and two multiparas, giving an incidence of 2.4 per cent. Four of these patients were given rectal ether with good results. Restlessness after delivery also was found but only in a few cases. Morphine  $\frac{1}{6}$  gr. hypodermically relieved this restlessness. Many women after delivery were quiet and asleep but were quite spastic and had a little tremor. This spasticity does not seem to be of any importance and soon passes away. The nurse is instructed to touch the patient as little as possible and to permit her to assume almost any position she wishes. She must be kept warm, however, and aroused and made to drink. She can even be given liquid nourishment before she is fully awake. It is difficult at times to tell when the patient is rational. Five patients were found out of bed after it was deemed safe to leave them. There were several minor accidents, such as abrasions of knees and elbows and in one case a ganglion of a wrist tendon. There were also two hematomas of the perineum following episiotomy which were discovered later than they would have been had the patient been awake, all of which shows that intelligent, careful nursing is quite essential.

There were three cases of aspiration pneumonia. All were mild and of short duration.

It has been our rule, however, that no patient shall be given the drugs if she has a full stomach. Stomach lavage was resorted to in several cases before the patient was given the nembutal.

In those cases (466) given gas at delivery the number of minutes required for analgesia and anesthesia were marked on each chart. We then drew from the files an equal number of charts of cases in which nembutal was not used. These charts show that an anesthetist attended the patients who were given nembutal an average of forty-six minutes each while the patients who were not given nembutal were attended an average of one hour and twenty-five minutes each. It shows also that the average time required for anesthesia was forty minutes in cases given nembutal and only thirty minutes in the cases which had none. This additional ten minutes probably represents the time used in preparing and draping the patient. Anesthesia is necessary when nembutal is used in order to control the aseptic technic. Information obtained concerning analgesia and anesthesia is found in Table XVIII.

During the puerperium 123, or 44 per cent, of the primiparas were catheterized an average of 5.8 days each and 43, or 19 per cent, of the multiparas were catheterized an average of 4.4 days each.

There was one maternal death and four fetal deaths, including all cases over five months, in the total of 500 deliveries. The mother's death could in no way be ascribed to nembutal. One baby had a large meningoencephalocele. The other three were obstetric fetal deaths. This gives a maternal mortality of 0.2 per cent, a gross fetal mortality of 0.8 per cent and an obstetric fetal mortality of 0.6 per cent. A comparison of these figures together with the operative incidence, and the figures from the same clinic covering the last five years and including this group of patients is given in Table XIX.

The gross fetal mortality should probably not be compared for very few patients having five and six months' miscarriages were given nembutal.

While these 500 patients were being delivered, there were 19 fetal deaths among 783 deliveries, 13 of which were unavoidable, composed of 10 prematures and 3 monsters. This gives a gross fetal mortality of 2.4 per cent. In some cases the attending man decided not to use any anesthesia when delivering a premature baby. It would, however, seem quite fair to make the above comparison of the obstetric fetal mortality rates.

TABLE XVIII. GAS ANALGESIA AND ANESTHESIA USED

	NO. CASES	ANALGESIA	ANESTHESIA	TOTAL	AVERAGE
Primiparas	254	With nembutal 52 hr. 25 min.	166 hr. 53 min.	219 hr. 18 min.	51 min.
	254	Without nembutal 287 hr. 52 min.	135 hr. 28 min.	423 hr. 20 min.	1 hr. 40 min.
Multiparas	212	With nembutal 57 hr. 30 min.	82 hr. 34 min.	140 hr. 4 min.	39 min.
	212	Without nembutal 134 hr. 16 min.	98 hr. 56 min.	233 hr. 12 min.	1 hr. 6 min.
Total	466	With nembutal 109 hr. 55 min.	249 hr. 27 min.	359 hr. 22 min.	46 min.
	466	Without nembutal 422 hr. 8 min.	234 hr. 24 min.	666 hr. 32 min.	1 hr. 25 min.

TABLE XIX

	FIVE-YEAR PERIOD	500 CASES WITH NEMBUTAL
Operative incidence	47.0 %	69.0 %
Maternal mortality	0.19%	0.20%
Gross fetal mortality	4.1 %	0.80%
Obstetric fetal mortality	1.2 %	0.60%

TABLE XX. MORBIDITY

Total cases reported	500
Number showing fever (American College of Surgeons standard)	20
Percentage of total	4%
Primiparas	16
Multiparas	4
Operative delivery	19
Spontaneous	1
Cause of Fever:	
Admitted with pyelitis	1
Admitted with phlebitis	1
Pelvic infection	10
Hematoma of perineum	2
Mastitis	2
Respiratory	3
Pyelitis postpartum	1
Total	20

During the past eight months we have both been doing a scratch test, using nembutal and scopolamine, on all patients. We have feared that some patient would be given the drugs who might be highly sensitive to one or both of them. So far we have found no one giving evidence of such sensitiveness either with the scratch test or by administration of the drugs. There were, however, 20 patients, or 4 per

cent, who slept from twelve to nineteen hours, or an average of fifteen hours, after being delivered. Since the average patient slept only five and one-half hours after delivery, these 20 patients evidently had difficulty in eliminating the drugs. It is evident that they represent a very small percentage.

It has been stated that such drugs will increase morbidity following contamination while restless and because of respiratory complications. In this series of 500 cases the morbidity according to the American College of Surgeons standard, which is now the same as the British standard, was only 4 per cent. Following the same standard the morbidity at the Evanston Hospital during 1932 was 3.4 per cent and during 1933 it was 5.5 per cent. None of the cases included in this group was severe. All but three had been discharged by the fourteenth day. One was discharged the fifteenth day and two on the eighteenth day. The morbidity is given in Table XX.

### CONCLUSIONS

1. Nembutal and scopolamine were used to allay the pain of labor in 500 cases, with successful results in 93.6 per cent.

2. Maternal mortality and morbidity are not increased.

3. Infant mortality and morbidity are not increased.

4. Operative incidence is increased but the increase is almost wholly confined to outlet forceps and is due to failure of cooperation by the patient because of the drug. This appears inseparable from any effective method of pain relief.

5. The method was used in 63.8 per cent of the women admitted while this study was in progress. This method, in common with all methods of pain relief, is not universally applicable. Whether it should be given or withheld should be decided by the obstetrician.

6. Constant and intelligent observation of the patient during and for some time after labor is essential. It is, therefore, a procedure for the well-organized hospital only. It should not be used in the home.

7. Our results with this method have been sufficiently satisfactory to warrant its further use.

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De Sa, H. D.: Some Characteristics of the Indian Pelvis, J. Univ. Bombay 1: 171, 1933.

The author studied the differences between the European and Indian races, with the hope of finding some definite factors regarding the size, shape, and development of the Indian pelvis that might explain the causes of fetal and maternal dystocia in Bombay. From his study he was able to draw the following conclusions: (1) The Indian pelvis is round as compared with the European oval pelvis; (2) the external diameters of the Indian pelvis give no certain criteria for the internal measurements of the true pelvis; (3) spontaneous labor may be expected through the Indian pelvis with an external conjugate of 15 or 16 cm.; (4) since the Indian fetus is relatively small, the cranial bones are softer and mould easily; therefore, trial labors are justified in many cases.

F. L. ADAIR AND H. L. MICHEL.

## FOOT DROP COMPLICATING THE PUERPERIUM\*

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Lincoln General Hospital)*

FOOT drop appearing during the puerperium is an unusual complication and has usually been attributed to pressure exerted by the fetal head in its passage through the birth canal. It is our purpose to present three cases of this condition together with some evidence tending to show that other factors may be responsible for this annoying complication.

CASE 1.—Mrs. H. N. B., aged thirty, primipara. Pelvis slightly contracted at outlet. Antepartum course normal until the seventh month when edema of the lower extremities and tingling of the fingers developed. Blood pressure and urinary findings constantly within the limits of normal. Neurologic examination repeated at intervals was essentially negative for organic disease. Labor inaugurated two weeks postterm by rupture of the membranes. Diagnosis O. R. P. Duration of labor twelve hours. Delivery of 7-pound 12.5-ounce child effected by manual rotation of the head and midforceps. During delivery the patient's left foot slipped from the stirrup and the patient assumed an oblique position on the table. The left foot was then held by an assistant, whereas the right foot remained in the stirrup.

Twelve hours postpartum the patient complained of numbness of both lower limbs and inability to flex the feet. Neurologic examination showed all reflexes to be equal, plantar irritations caused plantar flexion. Touch and pain sensations were undiminished over the dorsum of both feet and legs. Neither the right nor the left foot could be flexed. All other motions were normal. A definitely tender area was described just over the head of the fibula on the right leg.

Treatment upon the suggestion of one of us,† consisted in posterior molds, and braces affixed to the shoes as soon as the patient was up. On the eleventh day postpartum the left foot was improved markedly but there was no improvement noted on the right. The tender area over the head of the fibula remained for five months but at four months improvement had progressed to the point wherein the patient could walk without braces and the foot drop was scarcely notable. Ten months later the patient was seen by Dr. Norman F. Miller who reported that she still had a little difficulty in lifting the right foot, sensations were normal in both feet and there was no evidence of atrophy or underdevelopment of the right foot or leg. At this time there is no evidence of the previous trouble.

CASE 2.—Mrs. W. E. U., aged thirty, primipara. General physical examination revealed no abnormalities. Pelvic measurements within normal limits. During the last of her pregnancy there was marked edema of the lower extremities with some tingling of fingers. Blood pressure and urine were normal. Labor was induced by rupture of membranes and was short, first stage two and three-quarters hours, second stage one hour and seventeen minutes. Terminated by low forceps and

\*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.

†J. E. M. T.

episiotomy because of maternal exhaustion. The child weighed 7 pounds 6¾ ounces and the patient was in the stirrups approximately one hour. On the following morning a left foot drop was noted. Treatment closely corresponded to that of Case 1. Improvement was gradual and complete.

CASE 3.—Mrs. D. W. W., aged thirty-six, primipara. Antepartum course normal. Labor prolonged due to posterior position of occiput (O. R. P.). First stage, twenty hours. After five hours of second stage pains, version and extraction with forceps to after-coming head, effected delivery of a nine-and-one-half-pound baby. Patient in stirrups about one hour.

The following morning (six to eight hours later), a left foot drop was noted. Consultation with one of us,\* developed the same treatment as in Case 1. Foot drop cleared up completely in eight to nine months.

#### HISTORICAL

In commenting on the condition, Williams<sup>1</sup> quotes the work of Hünerman, showing that the external peroneal nerve supplying the flexors of the ankles and extensors of the toes, receives fibers from the fourth and fifth lumbar roots. These fibers pass over the brim of the pelvis where they are exposed to danger from compression. The lower root components of the external peroneal nerve lie upon the piriformis muscle and are more protected. Williams believes that in the majority of cases the injury is the direct result of pressure by the child's head and only exceptionally by forceps.

Pollock<sup>2</sup> discusses injury to the peripheral nerves. He believes that paralysis of the peroneal nerve is caused by the application of forceps, but that it may occur exceptionally in cases of generally contracted pelvis, with prolonged, severe labor.

Kleinberg,<sup>3</sup> reporting two cases in both of which there was marked cephalopelvic disproportion and in which the foot drop was bilateral but more severe on one side, concludes that intrapelvic pressure explains the injury.

Lambrinudi<sup>4</sup> reports two cases of foot drop and offers certain criticism of the theories of intrapelvic pressure and finds it difficult to believe that the fetal head can press on the lumbosacral cord. This nerve lies tucked away in the angle between the sacral promontory and the sacral wing. When there is cephalopelvic disproportion almost all of the pressure must come on the sacral promontory and the pubic bones. Were pressure the mechanism, he believes that one could expect the paralysis to occur on the side where the occiput rested. In one of his cases the fetal position was O.L.A. and the paralysis was in the right foot.

Lambrinudi also refers to a paper read by Brooks before Guys Hospital Anatomical Association wherein it is pointed out that there is a rotation backward of the sacrum, the excursion being in some cases

\* J. E. M. T.



one-fourth of an inch. In difficult cases he believes that the excursion would be even greater, the backward rotation putting an extra stretch on the lumbosacral cord which is already known as one of the tautest nerves in the body. Further substantiation of these views, Lambrinudi feels, lies in the field of veterinary obstetrics and points to the occasional paralysis in cows, wherein the only movable joint in the pelvis is the sacroiliac.

Duncan<sup>5</sup> reports two cases of foot drop following laparotomy with the patient in the Trendelenburg position. He believes that the etiology lies in the pressure on the external peroneal nerve by the head of the fibula.

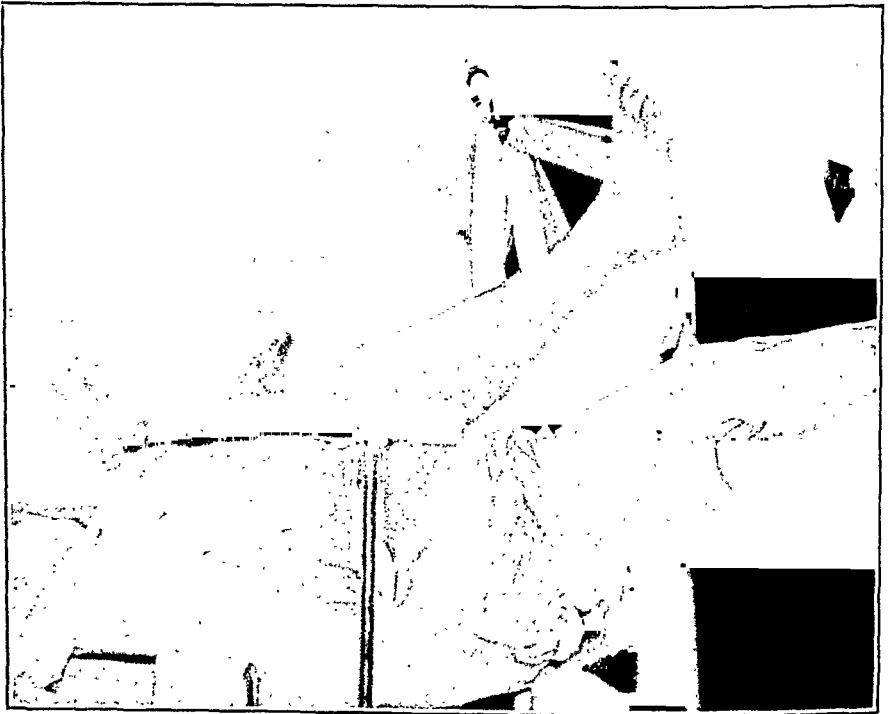


Fig. 1.—Showing point of contact of leg and stirrup.

#### ANATOMICAL

In the consideration of the relation of the sacroplexus to the bony pelvis, we find that the plexus is formed by the lumbosacral cord and the anterior branches of the first sacral and portions of the second and third spinal nerves. The lumbosacral cord consists of the union of a part of the anterior branch of the fourth lumbar and the entire anterior branch of the fifth lumbar nerve. As these lumbar segments come down along the sides of the bodies of the lumbar vertebrae, they are well protected from all possible pressure by the convex bony structures of the sides of the transverse processes. As they pass into the pelvis to join with the sacral branches their position is continuously protected by

the concave bony depressions and overlying muscle in the region of their foramina of exit into the pelvis from the sacrum. The plexus lies against the posterior wall of the pelvic cavity and rests upon the anterior surface of the pyriformis to pass out of the pelvis under protection of the greater sacrosciatic foramin. It is covered anteriorly by the pelvic fascia, which separates it from the internal iliac vessels, the ureter, and the pelvic colon. The peroneal nerve has its origin in the lumbosacral plexus, receiving fibers from the fourth and fifth lumbar and the first and second sacral to become part of the great sciatic nerve, until it is divided into the popliteal space to descend obliquely outward and downward to a very superficial position around the head of the fibula, there giving off its numerous branches to the anterior surface and muscles of the leg.

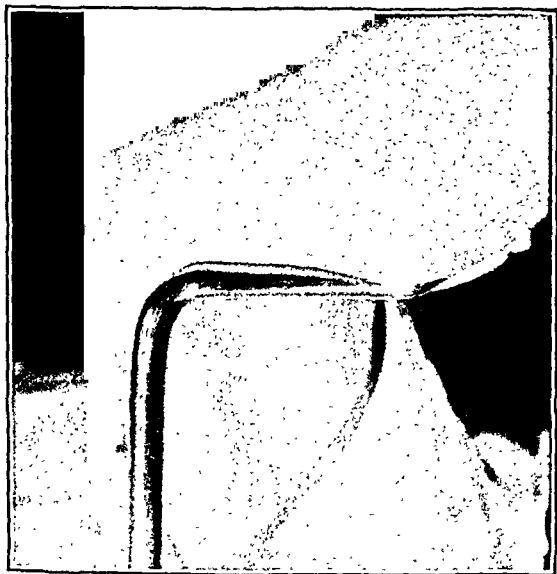


Fig. 2.

Fig. 2.—Detail of Fig. 1. Stirrup bar unpadded.

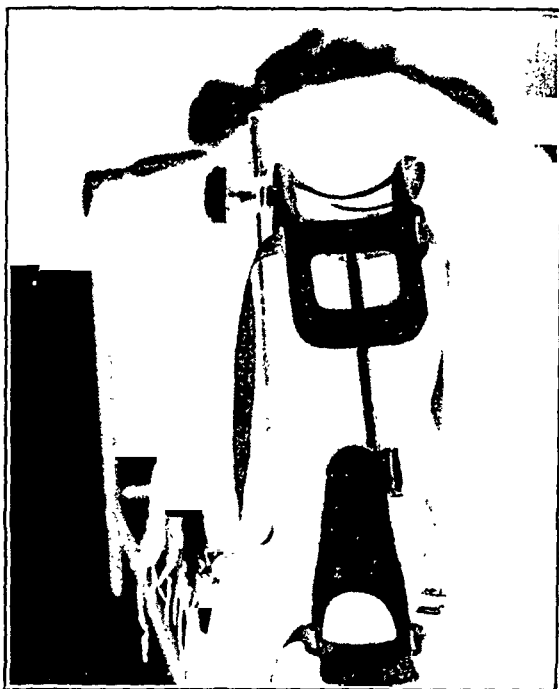


Fig. 3.

Fig. 3.—Gilbert-Kloman knee and foot support.

#### DISCUSSION

Foot drop is not an unusual complication in fractures of the head of the fibula or in wounds in this region. It is seen following the improper application of support about the knee while the patient is on the fracture table in traction for the application of a plaster cast, and pressure about the head of the fibula caused by improperly padded casts, a rubbing side arm or strap of a brace often causes this deformity.

In Case I, the striking fact was the point of tenderness over the head of the fibula. When the oblique position of the patient on the

table was approximated, this point coincided with the point of contact of the patient's leg and the transverse arm of the stirrup support (Figs. 1 and 2). It is also significant that the foot drop was most severe on this side. Cases 2 and 3 were likewise in stirrups, and although there was no evidence to show direct pressure on the nerve, yet we know that pressure on the nerve produced by rotation of the head of the fibula is sufficient to produce palsy.

With the protection afforded the sacroplexus as we have already pointed out, it is difficult to conceive how sufficiently direct pressure could be brought to bear by the presenting part in the pelvis without first doing irreparable damage to vascular and ureteral structures as well, and particularly why such a pressure should not involve fibers



FIG. 4.—Support padded.

that go into the formation of the tibial nerve which arises, not only from the fourth and fifth lumbar but also from all of the sacral nerves as well.

Convinced, in our own minds at least, that we were dealing with a peripheral nerve injury, treatment was instituted designed to give support to the affected members until such a time as regeneration would occur. The results of this simple treatment were most gratifying. In order to prevent repetition of this unfortunate complication, the Obstetrical Department of the Lincoln General Hospital adopted the Gilbert-Kloman surgical support, a knee crutch and foot support which does not permit of either release of the patient's foot during delivery or rotation of the head of the fibula (Figs. 3 and 4). This support was recommended to us by Dr. Jennings Litzenberg, and we have found it entirely satisfactory.

## SUMMARY

We feel, that in the cases herein presented, the etiologic factor of the foot drop was direct pressure on the external peroneal nerve. It is not our purpose to refute the various theories of eminent authorities with respect to this condition, but merely to offer evidence in support of an explanation that seems to answer the question of what caused these symptoms in this particular group of cases. It is undoubtedly true that in certain cases, a badly managed forceps operation on a floating head might permit of direct trauma to the sacroplexus due to the forceps blades, but it is our belief that in such an event, the paralysis would be more extensive, involving more muscles of the extremity, because of the probable impairment of the tibial nerve, and that there would be some permanent injury in the nature of residual foot drop, gluteal and tibial muscle atrophy as well as sensory changes.

## CONCLUSIONS

1. Three cases of foot drop occurring immediately after delivery are reported.
2. Direct pressure on the external peroneal nerve either by external force or by rotation of the head of the fibula, a mechanism not heretofore considered, is the probable cause of many of these accidents.
3. Pressure by the presenting part is an unlikely etiologic factor, particularly in view of the anatomical protections offered the sacroplexus.
4. A satisfactory foot and knee support is mentioned.

We desire to thank Dr. E. M. Hansen of Lincoln, Nebraska, and Dr. C. K. Gibbons of Kearney, Nebraska, for their permission to report Cases 2 and 3.

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- (1) *Williams*: Obstetrics, Ed. 6, Baltimore, Williams & Wilkins Co., p. 1111.  
 (2) *Pollock*: Curtis: Obstetrics and Gynecology 3: p. 1119. (3) *Kleinberg*: Surg. Gynec. Obst. 45: 61, 1927. (4) *Lambrinudi*: Brit. J. Surg. 12: 47, 1925.  
 (5) *Duncan*: J. A. M. A. 76: 23, 1921.

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Beaufays, J.: Habitual Hydramnion, Monatschr. f. Geburtsh. u. Gynäk. 97: 221, 1934.

According to Beaufays there are only six reports in the literature including his own case in which habitual hydramnion occurred. Among the maternal causes are given placenta previa, a large placenta, and nephropathy of pregnancy. Among the fetal causes are repeated occurrence of hydrocephalus, repetition of fetal hydrops and alterations in the umbilical cord. All the children in the reported cases were born dead and macerated. There was only one maternal death and this occurred in a case of placenta previa. The exact etiology and proper treatment of this condition are still obscure.

J. P. GREENHILL.

## COLPOCLEISIS IN THE TREATMENT OF UTERINE AND VAGINAL PROLAPSE\*

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A SURVEY of the American literature concerning the operative treatment of genital prolapse indicates that although many operative procedures have been considered, the colpocleisis methods have been largely discarded in recent years.

Payne<sup>1</sup> considered colpocleisis as unwise surgically and utilized the abdominal approach for the treatment of prolapse occurring after total hysterectomy. Phaneuf<sup>2</sup> felt that the modified Le Fort technic served well in a limited number of cases where the general condition of the patient prohibits extensive vaginal procedure. This author mentioned a series of 11 Le Fort subtotal colpocleisis operations and one total colpocleisis operation which formed the basis for his analysis. Baer and Reis,<sup>3</sup> in studying the results of 212 cases of uterine prolapse, found that the vaginal occlusion method of Le Fort had been the operation of choice in 14 cases. They concluded that this method of operative treatment was one of the four best suited to meet particular indications. Gellhorn<sup>4</sup> has spoken highly of the Le Fort procedure, and believed that the oblivion into which it has fallen is undeserved. Recently Simon<sup>5</sup> has collected 90 cases of subtotal and total colpectomy from the literature to which he has added 2 cases. He found that these operations were easily performed, yielded good results, and were safe.

The foreign literature contains more reference to the colpocleisis operations than does the American. The operation was performed first by Gerardin in 1823 in a modified form. Neugebauer performed his first colpocleisis in 1867, describing it in 1881. In 1877, Le Fort<sup>6</sup> described the operation which bears his name. Cotte and Creyssel<sup>7</sup> have described the technic of the Le Fort operation and list 12 such operations performed. Brocq and Nora<sup>8</sup> praised the Le Fort method as suitable in cases of total prolapse where there is ulceration and irritation of the prolapsed parts. Brocq and Nora<sup>9</sup> have studied the results of this modified Le Fort technic in 38 cases, ranging in age from fifty-two to seventy-five years. Petit-Dutaillis<sup>10</sup> has advanced a technic based upon the original Le Fort method, but with modifications, which he considered suitable for the treatment of prolapse. Bano<sup>11</sup> in a review of the various operative methods of treating uterine prolapse, has selected the Le Fort technic in 8 instances without mortality, complication, or recurrence. Labhardt<sup>12</sup> analyzed the results in 127 cases of colpoperineocleisis, operated by a somewhat different technic. Using local anesthesia, he obtains satisfactory results with a mortality of 1.6 per cent. This writer has abandoned the Le Fort method because of cases of urinary incontinence which have arisen, presumably due to traction upon the compressor urethrae. Rotter<sup>13</sup> described the technic of an artificial narrowing of the vagina, which has the advantages of preserving the sexual function of the vagina, and of permitting access to the cervix of the retained uterus. Serebroff<sup>14</sup>

\*Read at a meeting of the Central Association of Obstetricians and Gynecologists. November 1 to 3, 1934, New Orleans, La.

avored the total removal of uterus and vagina by a method in use in Russia since 1916. He reported on 23 patients operated upon since 1924 with favorable results in those followed up. Dujarier and Larget<sup>15</sup> described the operative technic of total colpectomy which they prefer in the treatment of prolapse in elderly women. Fabricius<sup>16</sup> has developed a modified total colpocleisis and perineoplastic operation in which the uterus is retained.

From these reports, it can be noted that in America colpocleisis methods have fallen somewhat into disfavor, and are relatively little used, while in the European centers there is a varied opinion as to the relative merits of the subtotal and the total types of operation. It was felt that an analysis of a series of colpocleisis operations from one clinic might be of value, both in determining the usefulness of the operation and in obtaining information as to the frequency of its employment.

This study comprises a five-year survey of all operations for genital prolapse at the Michael Reese Hospital, Chicago, with an analysis of those cases treated by any of the colpocleisis operations. During the five-year period 1929 to 1933 inclusive, there were 207 patients operated upon for genital prolapse. Of these, 167 patients were treated primarily for the prolapse, and 40 were treated for prolapse secondary to some other gynecologic condition, the prolapse operation being combined with operative treatment of the primary condition. Of these 207 patients operated upon for prolapse, 20 or 9.6 per cent were treated by some type of colpocleisis operation. This series of 20 cases forms the basis of the analysis in this study. The colpocleisis methods may be divided into two groups: subtotal and total. The subtotal colpocleisis methods accord with the technic of Le Fort or are modifications thereof. Total colpocleisis implies complete surgical closure of the vagina, and has been designated colpectomy by Simon and others. In this series there were 19 subtotal (9.1 per cent) and one total (0.48 per cent) colpocleisis operations. The uterus had been previously removed in 3 patients operated upon by subtotal method (twice by subtotal hysterectomy and once by vaginal hysterectomy); it was removed simultaneously with the vaginal occlusion in one case (by vaginal hysterectomy), and was left in situ in 15 cases. The total method usually implies previous or simultaneous removal of the uterus. In the case in this series the uterus had been previously removed by vaginal hysterectomy.

*Indications.*—The gynecologic indications for colpocleisis operations included the usual pathologic conditions accompanying prolapse. Prolapse without other significant findings occurred 6 times. Prolapse with cystocele occurred 3 times. Prolapse with attending cystocele and rectocele was the most common finding, occurring 7 times in the series. There were 4 cases of recurrent vaginal prolapse after previous removal of the uterus. The degree of prolapse present was indicated in the records as first, second, or third degree. First degree prolapse included those cases in which the cervix

descended to the level of the ischial spines. Second degree designated those cases in which the most dependent portion descended from the level of the ischial spines to the vulvar outlet. If any portion of the uterus protruded beyond the vulvar outlet, a third degree prolapse was present. Cases of excessive hypertrophic elongation of the cervix do not fall within this classification. According to this classification, in this series there were no cases of first or second degree prolapse, 16 cases or 80 per cent third degree prolapse, and 4 cases or 20 per cent recurrent vaginal prolapse.

*Medical Complications.*—The group of patients in which colpocleisis is indicated comprises the elderly women, usually past the menopause, in whom the sexual function can be disregarded. In this group are found many patients suffering from medical complications classifying them as poor surgical risks. Eleven patients in this series, or 55 per cent, were found to have such medical complications. It is in such cases of poor surgical risks that the colpocleisis operations are particularly adaptable, due to their relative simplicity in technic and to the fact that other forms of anesthesia than inhalation narcosis may be utilized. The following medical conditions were present: Myocarditis, 3 cases; myocarditis and hypertension, 3 cases; arteriosclerosis and hypertension, 4 cases; and thyrotoxicosis, 1 case.

*Age Incidence.*—The age incidence in the series under consideration may be expected, by the nature of the operation, to be rather higher than that of the usually operated groups. The youngest patient operated upon by this form of operation was fifty-three years, and the oldest seventy-two years (2 cases). The average age of all patients in the series was 62.6 years. This advanced age average, as well as the high percentage of medical complications encountered, contributes to the surgical risk hazard.

*Anesthesia.*—The choice of anesthesia in the series is of importance. In 8 cases of the 20 (40 per cent), ethylene anesthesia was used alone. In 2 cases (10 per cent), spinal anesthesia was utilized. Local infiltration only was the method of choice in 4 cases (20 per cent). Preliminary medication with scopolamine and morphine without anesthesia was possible in 3 cases (15 per cent). Morphine-scopolamine medication followed by local infiltration anesthesia at the time of operation was used in 2 cases (10 per cent). In one case (5 per cent) spinal anesthesia was only partially successful, and ethylene was used as an adjunct anesthetic. The anesthetic agent in the spinal anesthesia used in the series was nupercaine, introduced immediately before the operation by the usual technic of mixing it with the spinal fluid within the introducing syringe. The morphine-scopolamine premedication technic consisted in the administration of one-sixth gr. of morphine sulphate and  $\frac{1}{150}$  gr. of scopolamine hydrobromide administered one-half hour before operation, and the medication repeated in selected cases as the patient left for the operating room. This second dosage was omitted whenever there was a marked reduction in respiration rate, below 15 per minute after the first administration. One per cent procaine solution containing 4 minims of 1:1,000 adrenalin solution per ounce was used as agent for the local infiltration operations in the series. It may be noted that in only 40 per cent of the series was general anesthesia alone used; in all the remaining cases other forms of anesthesia were used in preference to inhalation narcosis.

*Technic.*—The technic of operation in this series was of necessity slightly varied, inasmuch as several different operators were at work. The technic herein described is that evolved by the senior author of this communication and represents his development of the generally used methods.

After cleansing and antiseptic preparation, anesthesia is induced. The final local preparation consists in instillation of one-half strength tincture of iodine into the vagina by means of an ordinary medicine dropper. A few drops spread over the vaginal mucosa with the fingers are sufficient to cover all folds of the mucous mem-

brane. If local infiltration anesthesia is utilized, the 1 per cent procaine solution is injected in liberal quantities beneath the vaginal mucosa anteriorly and posteriorly, particular care being taken to inject enough in the vaginal fornices and especially laterally into the cardinal ligaments and levator ani muscles. The perineum may be infiltrated at this time or it may be treated later.

It must be borne in mind that the objective of this procedure is to unite the anterior and posterior vaginal walls and at the same time to provide a trough extending from the external os symmetrically first laterally and then downward and outward to the vulva for the escape of uterine and cervical secretion. The amount and character of these secretions vary greatly; the atrophic senile uterus frequently producing little or no secretion, but occasionally these same senile changes resulting in stenosis of the cervix with pyometra, and in other cases erosion and ulceration of the cervix offering a real problem in the matter of adequate drainage. Excessive secretion from whatever cause should be controlled by appropriate treatment, whenever possible, previous to the operation. Dilatation of the cervix to permit drainage where stenosis exists, and rest in bed with the maintenance of reposition of the prolapsed uterus for ulcerated conditions of the mucosa usually suffice. Applications of mercurochrome and the use of a tampon to insure reposition are useful. Operation in the presence of infection or ulceration of the vaginal mucous membrane will most certainly result in separation of the sutured tissues, regeneration of mucosa, and complete failure of the operation.

It must be further borne in mind that the prolapsed structures form an almost shapeless mass which varies greatly in individual cases in reference to degree of hypertrophy and density of structures, presence or absence of cystocele, rectocele and vaginal hernias. Some degree of enterocele occasionally accompanies the complete prolapse. When a peritoneal sac is found, it is carefully isolated by dissection, and after ligating the neck as high as possible, the sac is removed. No serious difficulties arise in any step of the operation, and yet each detail must be executed with great precision if union of tissues, upon which the success of the operation depends, is to be attained.

The principle of the procedure is the very simple one of removal of a large rectangular oblong strip of mucous membrane from the anterior and posterior vaginal walls, and, by obtaining union of the underlying denuded tissues, the partial obliteration of the vagina and at the same time, as mentioned above, the maintenance of adequate drainage. The cervix is grasped with the tenaculum forceps and pulled downward so that the full extent of the prolapse is appreciated. The posterior vaginal flap is first outlined, beginning with the transverse incision about 2 cm. from the external os. This incision forms the narrow upper boundary of the rectangular flap obtained by uniting it with two longitudinal parallel incisions extending upward from the perineum. The perineal ends of the longitudinal incisions are united by means of a transverse incision, thus completing the rectangle. The size of the flap depends upon the size of the vagina and the degree of the prolapse, but it may be made from 4 to 6 cm. in width, and it extends to the vulvar outlet. In removing the vaginal flap, the tissues must be kept taut by traction with tissue or artery forceps. If the delineating incisions be carefully made, the planes of cleavage will be entered and the denudation more easily attained. Individual ingenuity is a factor in the execution of the details of the various steps. Entrance into the peritoneal cavity should be avoided in denuding the posterior area, as the tissues are often very thin and ill defined and the culdesac of Douglas may readily be entered. After the posterior area is denuded, the cervix is drawn downward and posteriorly exposing the anterior wall. Here in like manner, an exact duplicate of the posterior rectangular flap is removed, overlying the bladder, and extending from 2 cm. from the external os to approximately 2 cm.



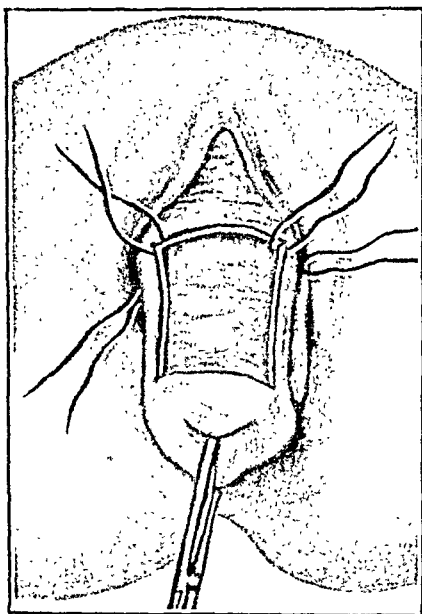


Fig. 1.

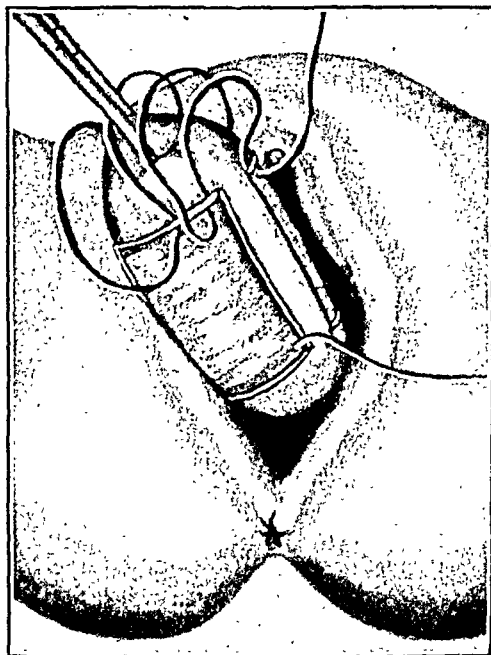


Fig. 2.

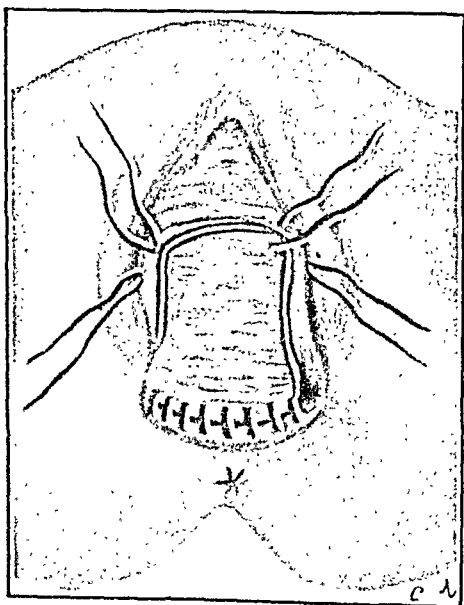


Fig. 3.

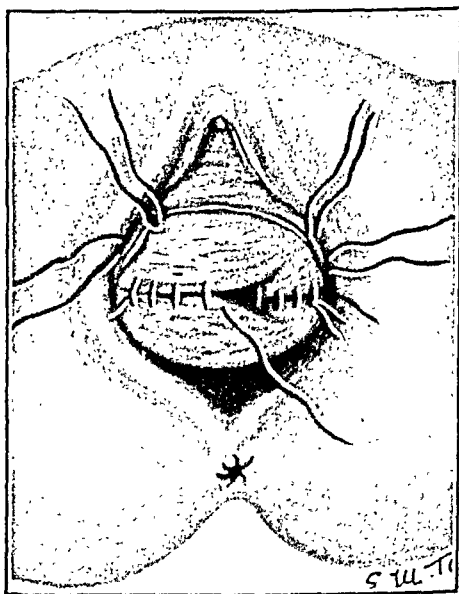


Fig. 4.

Fig. 1.—Subtotal colpocleisis. Completed denudation of anterior and posterior oblong vaginal strips. Anterior denuded area is in full view, posterior area may be seen to the right and behind it. Cervix is pulled downward and posteriorly so that full extent of the prolapse may be appreciated. (E. M. Tate after Cotte and Creyssel.)

Fig. 2.—Subtotal colpocleisis. Cervix is pulled anteriorly and toward operator's left. Anterior and posterior areas are denuded. Sutures uniting cervical borders of the denuded areas are partially completed. When pulled taut, these sutures invaginate the cervix and form the transverse trough below cervix.

Fig. 3.—Subtotal colpocleisis. Transverse trough is formed by completion of first row of sutures. Cervix is entirely invaginated. Longitudinal troughs are about to be formed. (E. M. Tate after Cotte and Creyssel.)

Fig. 4.—Subtotal colpocleisis. Second row of sutures uniting anterior and posterior vaginal walls is in denuded areas. This row further invaginates the vagina. Successive rows of sutures are introduced until the entire vagina is invaginated. (E. M. Tate after Cotte and Creyssel.)

from the external urinary meatus. After both areas are prepared, the edges of the remaining mucosa are undermined a short distance in order to mobilize them for future suturing. For suture material No. 2 chromic catgut is used, and the continuous suture will avoid the burying of any knots. Succeeding steps may be better understood by consulting the accompanying illustrations in which the further details are described.

Total colpocleisis is performed when complete prolapse of the vagina with or without enterocele following vaginal hysterectomy is encountered. In these cases the problem is simplified because it is unnecessary to provide drainage. The vaginal mucosa is divided longitudinally in the median line from the perineum to a point 1 cm. below the external urinary meatus. The entire vaginal mucosa is detached by

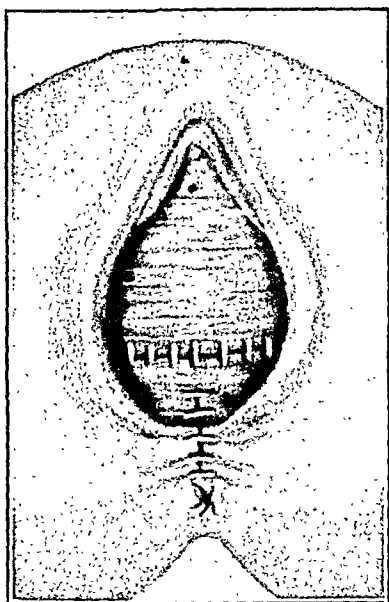


Fig. 5.

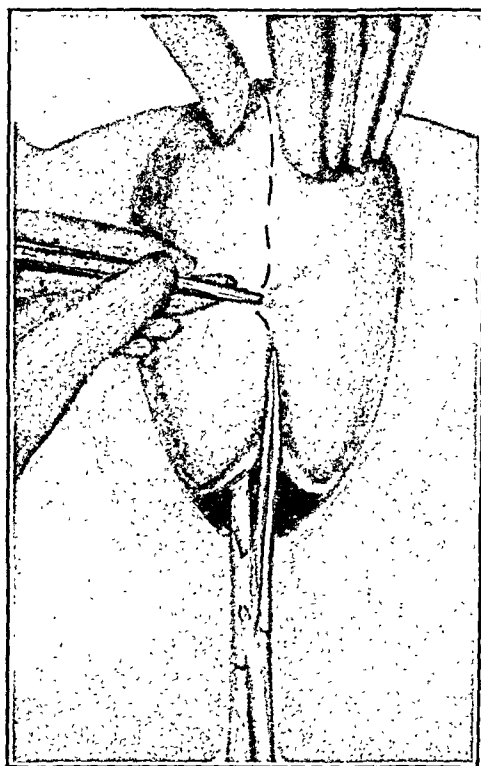


Fig. 6.

Fig. 5.—Subtotal colpocleisis. Vagina entirely invaginated and lower edges of denuded areas are approximated. Perineorrhaphy is completed. More extensive closure of the vulva, than here shown, should be secured by a simple modification of the perineal repair. Longitudinal troughs appear at the ends of the transverse suture line. (E. M. Tate after Cotte and Creyssel.)

Fig. 6.—Total colpocleisis. Median longitudinal incision through vaginal mucosa, beginning posteriorly.

sharp dissection, working laterally from the longitudinal incision. If a hernial sac is encountered, it is isolated and removed as described.

Such vestiges of the levator ani muscles and fascia and urogenital septum as can be found in these senile patients are united in the median line in an attempt to reform a pelvic floor and obliterate the vagina. This step in the operation should be performed with a finger in the rectum so that all available structures may be completely utilized, and at the same time the rectum itself carefully protected from injury. The enormous area of detached vaginal mucosa is ablated, leaving only enough to cover the defect. Approximation of the mucosa and perineum completes the operation.

*Mortality and Morbidity.*—Gross morbidities were calculated on the basis of one or more temperature readings of 101° F. by mouth during the postoperative course. Corrected morbidities excluded those cases with such readings unaccompanied by recognizable pathologic changes and depended upon definite clinical findings and diagnoses. The number of patients requiring one or more catheterizations was also calculated, although a high percentage might be expected from such a group and in view of the type of operative procedure undertaken.

There were 3 postoperative deaths in this series. The first of these occurred twenty-four days after operation in a sixty-three-year-old patient. A vaginal hysterectomy followed by subtotal colpocleisis was performed under spinal anesthesia. The patient had as medical complications hypertension and chronic myocarditis. On the ninth postoperative day the temperature rose to 103° F., and the pulse became ir-

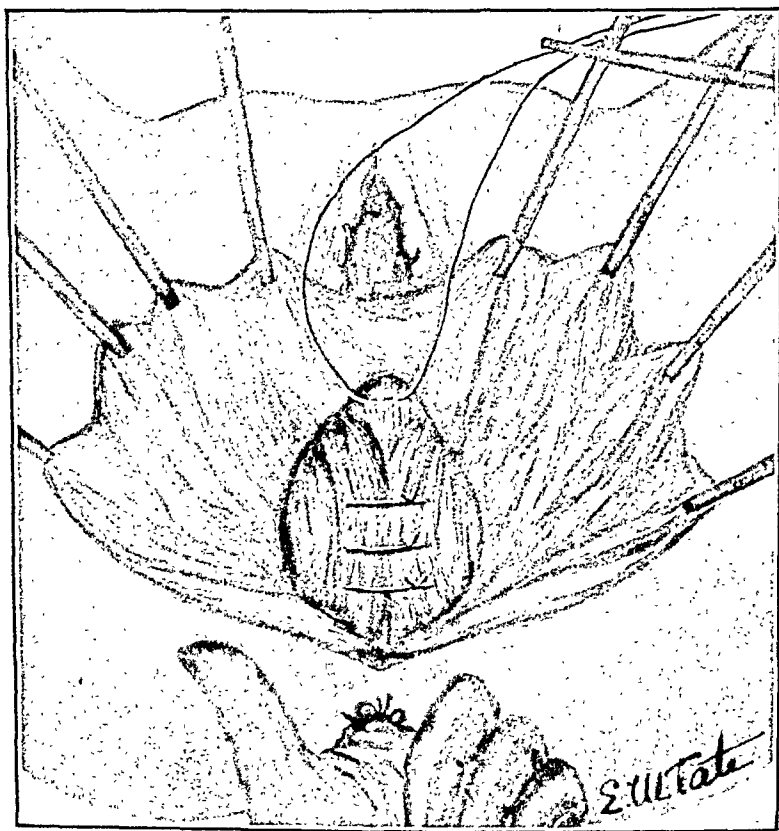


Fig. 7.—Total colpocleisis. Vaginal mucosa with vaginal fascia is being detached. Pelvic floor is being restored by uniting levator ani muscles in midline.

regular and rapid. Auricular flutter was noted on the next day, and on the thirteenth postoperative day the diagnosis of right lower lobar pneumonia was made. The patient continued in very poor condition with rapid pulse and high fever until the twenty-fourth day when she died. The final diagnosis was that of postoperative lobar pneumonia. The second fatality occurred in a seventy-two-year-old woman suffering from thyroid enlargement, hypertension, and cardiac hypertrophy in addition to third degree prolapse. A Le Fort subtotal colpocleisis and perineorrhaphy were performed under local infiltration anesthesia. Within twenty-four hours after operation the temperature rose to 104° F. and the pulse to 144. The patient became stuporous, the temperature continued to rise, and the pulse became thready and weak. The patient died about twenty-six hours after operation. An acute thyroid crisis was considered as a cause of death because of the enlarged thyroid gland, and

the possibility of a cerebral accident was also considered. A complete postmortem examination revealed among other findings: bronchopneumonia, ulcerating adenocarcinoma of the corpus uteri, severe compression of the trachea by an adenoma of the thyroid gland, and generalized arteriosclerosis with cardiac hypertrophy and dilatation. Death of the patient was presumed to be due to bronchopneumonia. The third death occurred in a sixty-six-year-old woman, with hypertension and arteriosclerosis and complete prolapse. A Le Fort subtotal colpocleisis and perineorrhaphy were performed and the patient progressed entirely satisfactorily until the sixth postoperative day when she became cyanotic, dyspneic, with increased pulse rate and respirations. The patient became comatose and died within three hours of the first alarming symptom. The diagnosis made was that of pulmonary embolism.

The gross morbidity in the series totaled 3 cases or 15 per cent, the corrected morbidity 5 per cent. Nine patients (45 per cent) required catheterization. The average hospital stay of the patients in the series was fifteen days.

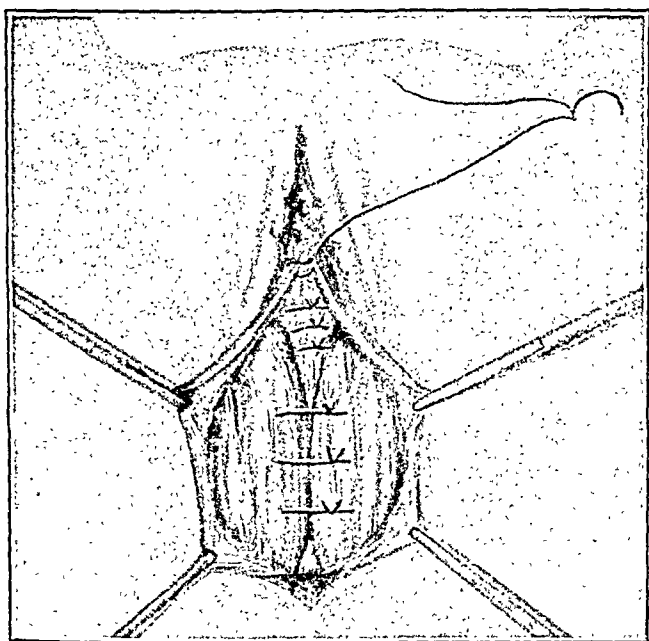


Fig. 8.

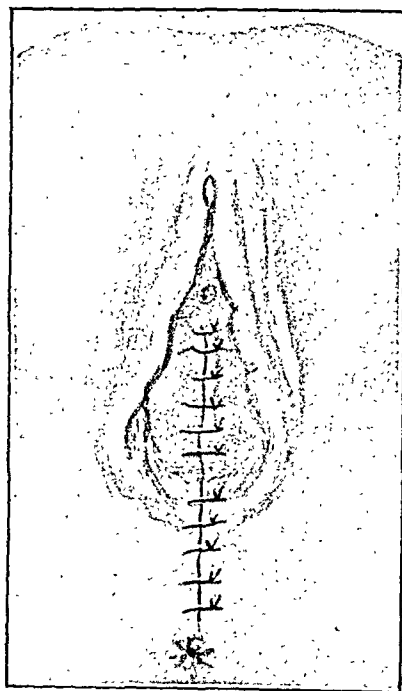


Fig. 9.

Fig. 8.—Total colpocleisis. Prolapsed vagina is ablated. Levator ani muscles and fascia and urogenital septum is united in midline, obliterating the tract occupied by the vagina.

Fig. 9.—Total colpocleisis. Operation is completed. Area may be closed over more completely by labial skin instead of utilizing cuff of vaginal mucosa.

The postmortem discovery of an unrecognized carcinoma of the corpus uteri in a patient subjected to subtotal colpocleisis with retention of the corpus, emphasizes the need for routine dilatation and curettage as a preliminary step immediately preceding performance of any of the colpocleisis methods which contemplates retention of the corpus. This need has previously been considered by Brocq and Nora,<sup>8</sup> by Phaneuf,<sup>2</sup> and by Simon.<sup>5</sup> Further, the advisability of performing vaginal hysterectomy combined with colpocleisis for the relief of prolapse may be open to question.

A word of caution is advisable in view of the fact that the literature on this subject speaks of uneventful convalescence and uniformity of good results. This is somewhat too optimistic. An occasional failure is unavoidable when the factors of advanced age and impaired nutrition and infection of the operative field are encountered.

Of the 17 surviving cases in the series, 16 were studied for various lengths of time after leaving the hospital. One failed to return for such follow-up study. All patients were examined either by the operator himself or by some member of the gynecologic staff. The duration of the follow-up varied from five weeks to four years and eight months after operation. Many of the patients were studied for long periods of time after leaving the hospital, the average duration of the follow-up study on the 16 patients being 46.3 weeks.

Of the 16 patients thus followed, 1 case showed an unsuccessful result. In this patient subtotal colpocleisis and perineorrhaphy were performed. Immediate convalescence was uneventful, but subsequent examination revealed complete separation of the anterior and posterior vaginal walls with regeneration of mucous membrane. With this one failure noted, there was a record of 6.2 per cent failure and 93.8 per cent success in the series.

#### SUMMARY AND CONCLUSIONS

1. Colpocleisis as a method of treatment of genital prolapse is useful in an appreciable percentage of all operated cases (9.58 per cent in this series).

2. The operation may be either subtotal, according to the Le Fort technic or modifications thereof, or total in nature. Total colpocleisis is performed after previous vaginal hysterectomy has been done.

3. Colpocleisis may be utilized in cases of uterine or vaginal prolapse occurring in elderly women, usually past the menopause, in whom the sexual function of the vagina may be disregarded. It may be the method of choice in this group of patients when prolapse occurs after hysterectomy.

4. The advantages of colpocleisis are: simplicity of technic, possibility of avoiding inhalation narcosis, high percentage of good end-results and permanence of cure, and the relative safety of the procedure in selected cases.

Acknowledgment is made to the members of the Gynecologic Staff of the Michael Reese Hospital for the use of their records.

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## THE THIRD STAGE OF LABOR\*

### RELATIONSHIP OF BLOOD LOSS TO PRECEDING LABOR PAINS

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IN THREE previous communications<sup>1, 2, 3</sup> the author has attempted to present an accurate knowledge of the physiologic factors governing the amount of blood loss in the third stage of labor and, thereby, to arrive at a more logical management of the parturient woman. This fourth contribution in the series is prompted by the well-established belief throughout the profession that prolonged labor due to poor labor pains, and secondary inertia due to exhaustion, are both likely to be followed by a large blood loss in the third stage because of the continued inability of the uterus to contract sufficiently to stop oozing from the maternal blood sinuses. The latest edition of Kerr and Ferguson's *Textbook*<sup>4</sup> italicizes the sentence, "We are absolutely satisfied that the three important causes of postpartum hemorrhage are faulty management of the third stage, unduly prolonged labor, and large doses of anesthetic and sedative drugs." DeLee's *Obstetrics*<sup>5</sup> states, "An exhausted uterus . . . may be attended by bleeding." Inasmuch as our experience has not been in agreement with these and many other similar statements in the obstetric literature, we are submitting the following summary of the relation between the character of the labor pains in the second stage and the amount of blood loss in the third stage. Inasmuch as the tonicity of the uterus sometimes changes as labor progresses, it was felt that a study of the correlation between second stage labor pains and blood loss would be more significant than the correlation between first stage pains and blood loss. There were available for this study some seven hundred consecutive labors in which full data as to the character of the pains and the amount of blood lost are available. The blood loss has been *measured and recorded* in the same manner as previously described.<sup>1</sup> The labor pains were analyzed and classified with respect to their frequency, duration and intensity. The intensity was determined by noting the degree of hardness of the uterine wall at a point on the fundus not directly over the body of the baby as described in a previous communication.<sup>6</sup>

\*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.

The information thus obtained was collected and classified as in Tables I and II. The results are quite apparent. In Table I it is quite evident that neither duration nor intensity of the individual pain has any effect whatever on the amount of blood lost in the third stage. At first glance it would seem that the frequent labor pain was conducive to a slightly greater blood loss (30 c.c.) than results when the pains are farther apart. This apparent small difference is probably not significant. The chance occurrence of one or two rather large losses in the small group of forty-seven patients could well account for the slight difference noted.

TABLE I. THIRD STAGE BLOOD LOSS IN RELATION TO SECOND STAGE LABOR PAINS  
MULTIPARAS

Frequency of Pains		
Less than two minutes apart	47 cases	185 c.c. average
Two minutes or more apart	196 cases	152 c.c. average
Duration of Pains		
Thirty seconds or less	89 cases	153 c.c. average
Thirty-five seconds or more	129 cases	165 c.c. average
Intensity of Pains		
Weak contractions	67 cases	165 c.c. average
Moderate or strong	190 cases	161 c.c. average

TABLE II. THIRD STAGE BLOOD LOSS IN RELATION TO SECOND STAGE LABOR PAINS  
PRIMIPARAS

Frequency of Pains		
Less than two minutes apart	61 cases	136 c.c. average
Two minutes or more apart	317 cases	198 c.c. average
Duration of Pains		
Thirty seconds or less	160 cases	216 c.c. average
Thirty-five seconds or more	180 cases	155 c.c. average
Intensity of Pains		
Weak contractions	123 cases	255 c.c. average
Moderate or strong	270 cases	155 c.c. average

Similar data on primiparas, Table II, shows a somewhat different picture. Here we find that poor labor pains are attended with greater blood loss than that noted with good labor pains. This is true whether we consider the frequency, the duration, or the intensity of those pains. Infrequent labor pains are followed by a 50 per cent greater blood loss than is present when the pains are close together. Short labor pains show a similar increase in blood loss when compared with long labor pains. It would seem that the intensity of the contraction is even more important, as here we find a difference of 100 c.c., on the average, between moderate or strong pains on the one hand and weak contractions on the other.

Why primiparas should show this characteristic when it is not present in multiparas we are, as yet, unable to explain. It was thought

that perhaps the greater incidence of episiotomy and deep second degree laceration might be a factor. Reassembly of the case records and analysis thereof, making full correction for both episiotomy and deep laceration, failed to substantiate this supposition, as it was found that no part of the difference could be ascribed to this cause. Operative delivery is somewhat more frequent in this "poor pain" group than when second stage pains are good, but, as previously reported,<sup>1</sup> operative delivery is not attended with as much difference in blood loss as that indicated in Table II due to the difference in the character of the labor pains. We use less anesthesia in spontaneous deliveries when the pains are poor than when they are good. Corrections for anemia and for such abnormalities as placenta previa, both of which occur more frequently in primiparas than in multiparas, were also made and found to have no effect on these averages shown in Table II. We are, therefore, unable to explain why primiparas do show this difference in blood loss definitely correlated with the character of second stage labor pains while multiparas fail to show a similar correlation. Perhaps it is something inherent in the primipara. Our previous studies<sup>2</sup> have shown that primiparas do not lose appreciably more blood than multiparas. We have been able to indicate<sup>1</sup> that there is no appreciable correlation between the duration of the labor (either first, second, or third stage) and the amount of blood loss. The only distinct difference between primiparas and multiparas which we are able to offer as an explanation at the present time, is that noted in our second communication with reference to the difference in blood loss produced by differences in the size of the baby and the size of the placenta in primiparas as contrasted with multiparas. It was noted in the Litzenberg series of cases that the large baby and the large placenta both produced a much greater increase in the blood loss in primiparas than did these same factors in multiparas. Whether large babies or large placentas are more conducive to poor labor pains in primiparas than in multiparas we do not yet know. Our "clinical recollection" would indicate this to be true, but clinical recollection with respect to labor has been so often proved in error that we hesitate to offer this as an explanation until further analysis of actual, carefully collected, records can be made.

It might be well to point out that this communication does not consider "exhaustion states" of the whole organism whether due to the labor or to general body disease. Assuming that any "uterine exhaustion" would be reflected in the uterine contractions, we have studied those contractions in their relationship to blood loss. Whereas, this is not a study of anesthetics, we recognize the importance of proper anesthesia and have routinely employed nitrous oxide-oxygen analgesia with as short anesthesia as possible. Proper management of the third stage of labor<sup>3</sup> dictates that one should discontinue the



anesthetic immediately following delivery of the child and reemploy it for repair of lacerations after delivery of the placenta and after establishment of good uterine tone.

#### SUMMARY

In our previous communications we have shown that parity of the mother has no effect on the blood loss in the third stage. Length of labor has also been shown to have no influence. The episiotomy adds about 60 c.c. of blood on the average blood loss. The relative loss with a large baby or a large placenta is about 100 c.c. more than with a small baby or small placenta. We have noted here in primiparas a difference between good pains and poor pains of about 60 to 100 c.c.; so that, while each of these factors is a definite one, it is relatively unimportant when compared with the difference between poor management and good management of the third stage (200 to 400 c.c. on the average). It might, therefore, be well to change Kerr and Ferguson's statement so that it would read, "We are absolutely satisfied that the two important causes of postpartum hemorrhage are faulty management of the third stage and large doses of anesthetic and sedative drugs."

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Pain in the genital tract of women is due to irritation of the nerves connected with voluntary actions and those associated with the vegetative system. But the two systems are interwoven. Thus pain in the region of the internal os of the cervix which is sympathetic in type, may be reflected to the small sciatic nerve and erroneously lead to a diagnosis of coxalgia. A sympathetic uterine pain may be reflected in the larynx, the heart or the stomach and, on the other hand, a pain in the genitalia may have a central origin, as for example in tabes. For morbid conditions it is important to investigate the individual's heredity. This will explain why in certain individuals inflammation and physical and chemical intoxications act more strongly than in other individuals.

Treatment should always take into consideration heredity even in surgery, and this is especially true in young women. To prevent pain in women and to diminish its intensity, it is essential to take good care early of young girls and to watch for the proper development of their genital apparatus.

J. P. GREENHILL.

## THE VALUE AND LIMITATION OF ROENTGEN RAYS IN OBSTETRICS\*

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ROENTGEN rays have been accepted for the past decade as adjuncts in the practice of obstetrics. The latitude of usefulness has been demonstrated in many unsuspected complications and it can be employed advantageously in every patient. Every one would not be materially benefited, but in the summation of abnormal findings, in a large series, the roentgen rays are unquestionably justified. One of us<sup>1</sup> in a previous communication reviewed the literature demonstrating its uses. It is not within the realm of this paper to repeat the history of roentgen ray development in obstetrics; but it is our desire to recall some of the uses and fallacies of our original viewpoints, and to stress the need for more widespread application.

The burden of proof of early pregnancy always has been placed upon the clinical ability of the physician. Often from overenthusiasm and to his chagrin, the practitioner has made himself liable. The old professional adage is, "Never implicate yourself; refrain from expressing an opinion. Time will tell!" This advice is acceptable in many cases; while in others, certain exigencies arise that demand a positive opinion. It is in this latter group that the Aschheim-Zondek test serves its purpose best. We are in accord with its value; but we are likewise cognizant of its fallacies. If in the face of repeated negative tests, clinical signs still suggest pregnancy, we advise a flat film with the patient in the prone position. This position usually identifies an earlier fetus than any other method, with the exception of pneumoperitoneum. When diagnosis is urgently needed for the consideration of therapeutic abortion, we advocate the use of intrauterine lipiodol injections. We do not advocate its general employment in uncomplicated cases, but we cannot recall any harm from its use. Abortion may follow. It is our observation that lipiodol invariably terminates pregnancy. The lipiodol solution demonstrates the change in contour and enlargement of the uterine cavity, the presence of intrauterine abnormalities and unquestionably demonstrates the presence of a normal cavity in a uterus enlarged from other causes.

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\*Read at a meeting of the Central Association of Obstetricians and Gynecologists, November 1 to 3, 1934, New Orleans, La.

The positive diagnosis of the death of the fetus either before or after viability is always difficult. Its importance has traditionally assumed unusual proportion, at least to us; for we have never seen a case followed by sepsis. Nature always hastily intervenes. However, it is of grave importance when termination of the pregnancy is contemplated; for a living fetus brings severe criticism. Lipiodol injections before the period of viability demonstrate the symmetrically enlarged uterine cavity with a mottled appearance. This is due to the penetration of the disintegrating fetus by oil. If the placental site is still intact, the symmetrical outline of the cavity will be broken by a gap, signifying that the solution has not encircled the cavity. It is rarely necessary to resort to lipiodol after the period of viability; for the fetal skeleton is usually demonstrated. The condition of the skull is indicated by loss of contour, by overlapping of suture lines and by the softened appearance of the cranial bones. During 1932 in thirteen suspected cases of death of fetus, the roentgen ray demonstrated suggestive evidence that the termination of pregnancy was clinically correct.

The enlarged abdomen or overdistended uterus offers a very fertile field for diagnostic speculation. Many times from obesity or overdistention of the uterus, it is impossible to define its contents. When the roentgen rays reveal an unusually large fetus or multiple pregnancy, the situation is relieved; but when polyhydramnios is present, the case assumes more importance because of its association with monstrosities. The flat film often will not disclose the exact contents of the uterus, but when a combined lateral one is made, a multiple pregnancy or a monstrosity will be picked up that otherwise would not have been seen. The recognition of this catastrophe with proper treatment instituted relieves many months of physical embarrassment and many hours of mental anguish. A suspected hydrocephalic monster with moderate hydramnios is a perplexing problem. Quite often the film will demonstrate the exact size of the cranial vault. In many cases the proper management will eliminate difficult dystocias or probably cesarean section.

Many times, cases have been admitted to our emergency service where delivery had been attempted. These patients were usually critically ill from exhaustion, dehydration, infection and occasionally with tetanic uteri with or without retraction ring. In a large group, the roentgen ray has been of value in disclosing the reason for dystocia. On several occasions the film presented evidence of the ring that checked with clinical findings. This ring was best demonstrated in the underexposed film. In the future it is our desire to study more dystocia of undetermined causes in an effort to reveal the so-called contraction ring; for it is not fantastical to believe that retraction rings are preceded by contraction rings. If such is demonstrated, early treatment would eliminate this serious complication.

On two occasions, the flat anteroposterior film revealed the uterus filled with gas. Routinely we take blood cultures on all emergency cases admitted to our service and have found a variety of organisms prior to the delivery. These manifestly direct our therapy before the infection has made such extreme inroads. In cases of gas bacillus infection recognized by gas within the uterus, perfringens serum could be administered early; and, by doing so, the efficacy of the serum would be immediately enhanced in place of waiting for the usual return from uterine and blood cultures. This would give the serum an unusual opportunity to combat the massive injection of organisms which are thrown into the circulation immediately following placental separation.

Nowhere within the realm of obstetric and gynecologic diagnosis, does the roentgen ray serve with more accuracy than in abdominal pregnancy. Contrary to the generally accepted symptomatology in the cases we have seen, the contour of the abdomen, the closeness of the parts to the examining fingers, the lack of contraction to the uterus, the movability of the fetus and even pelvic examination, has been of little value. The flat and the lateral film disclosed the presence of the fetus in the abdominal cavity; but failed to demonstrate whether intrauterine. The positive diagnosis of this serious condition was impossible; exploratory operation was necessary. This procedure quite often resulted in severe hemorrhage by the injudicious use of the exploring hand of the operator. Not until the use of lipiodol intrauterine injections with flat and lateral films were we able to say that we were actually dealing with a true abdominal pregnancy. Since that time, we have and shall continue to lower our extremely high mortality of the past decade. Since the exact position of the fetus and the uterus is definite, the hand need not be introduced into the abdominal cavity. The abdomen is opened by a wide incision, the sac punctured, the fetus removed and the placenta dealt with as seen fit. Criticism might be prompted by the introduction of this media into the uterus in a suspected case of abdominal pregnancy. We have seen no ill-effects other than an abortion; and, certainly this offsets the past high mortality and indiscriminate operating of the past few years.

The management of dystocia has been and still is an unsolved individual problem. The period of indecision often subjects the patient to an unnecessary hazard; for the relative period of safety has unfortunately passed. Many times clinical experience is unable to cope with this question, and therefore, every available means should be used to foresee or eliminate all possibilities. Previously one of us demonstrated the accuracy of roentgen ray pelvimetry by the use of the modified Thom's method. This procedure served as a valuable check on our previous pelvis estimations, but left us in the same quandary as prior to its use. We are indebted to the contributors who interested

us in roentgen ray pelvimetry and, are ever mindful of the scientific data accumulating in the study of distorted pelves. Trial and error have convinced us that no geometrical calculation with flat films, regardless of the method used can give us that desired information, whether or not the pelvis is sufficiently large to permit the passage of the fetus. Some time ago<sup>2</sup> one of us suggested the use of the combined flat anteroposterior and lateral film.

The flat film in the anteroposterior position is indispensable, for it demonstrates irregularities in shape, contractures of the pelvic inlet and position of the fetus. It aids in correlating the exact position in the study of the lateral film. The lateral film indicates the size of the true conjugate, the shape and contour of the sacrum and the posterior half of the pelvis; but most important, whether engagement has taken place and the degree of descent into the pelvis.

Most malpositions are initiated by distorted pelves. Recognized and corrected early, the problem is simplified. Early in the use of roentgen rays either before or shortly after the onset of labor, we detected the fallacy of prognosis from either the flat anteroposterior, lateral, or combined films. Many times these films presented such degree of malposition that delivery seemed impossible. To the surprise of the roentgenologist and ourselves many of such patients delivered spontaneously or required a simple vaginal maneuver. So that at present, when the presenting part is engaging well and descent is taking place (as shown by repeated lateral films) regardless of the position, we permit the patient to have an opportunity for vaginal delivery.

Moreover, maneuvers for the correction of malposition have been materially aided by a flat and a lateral film, because extreme molding and edema of the head often obscured the exact relation of the presenting part to the pelvis. Repeated films following the correction of malposition revealed whether the attempt was successful. The management of an impacted breech and even transverse presentation have been simplified by knowing exactly the condition to be dealt with before delivery was begun. Suspected cases of uterine abnormalities have been demonstrated before labor. This minimized the anxiety for the ultimate outcome.

Asynclitism has become recognized as one of the most important factors in prolonged labors. Serial lateral films have been of more value in recognizing and studying this mechanism than any other approach. For while pelvic examination can reveal the position, mechanism, and descent, it cannot tell just how much of the head remains above the inlet because of extreme overlapping and molding. The film demonstrates exactly the period of mechanism attempted and indicates how much time will be consumed before the termination of labor. It likewise directs the necessary operative maneuver in the event Nature fails.

During the conduct of labors in borderline pelves, flat and lateral films are repeated at four-hour intervals before any question of management is determined. More than once we have seen the initial film indicate an almost absolute disproportion only to be followed by a short, spontaneous delivery. On the contrary, we have seen unnecessary operative procedures carried out based on the initial flat film.

The information gained by the combined use of flat anteroposterior and lateral films renders assistance to all. It removes all geometrical calculations.

We are infinitely more interested in assembling methods that will be of more widespread use than complicated roentgen ray technical estimations. These estimations have eliminated the probabilities of its use other than in trained obstetric services. Roentgen ray technicalities have given a false sense of security to the profession; for while the roentgenologist and the general practitioner realize the value of roentgen ray prognosis, they omit the necessary details of this procedure either by lack of knowledge or failure of application. The average roentgenologist is giving a false sense of security to the profession by reading the simple flat anteroposterior film, and while it divides the responsibility of the clinician, it is guiding him into unnecessary radical procedure or advising him in cases that ultimately turn out to be difficult or almost impossible.

In the final analysis, roentgen rays must be used only as an adjunct and not to replace clinical ability. We conclude that repeated, combined flat anteroposterior and lateral films have been of more value and have given us a greater sense of security than any other method in solving the individual problem of dystocia.

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The incidence of abortion and miscarriage in the Philippine General Hospital shows a tendency to rise. Blood transfusion has greatly lowered the mortality from obstetrical complications that are accompanied by shock and hemorrhage. Placenta previa shows a high incidence among Filipinos, and is attributable to such predisposing causes as inadequate puerperal care; getting up, going about, and doing housework too early; and to the squatting habit of our women. There is great need for more widespread prenatal and postnatal care among Filipinos. Next to puerperal septicemia, puerperal hemorrhage shows the highest maternal mortality in the Philippine General Hospital and in the City of Manila.

C. O. MALAND.

# "PARAMETRIAL FIXATION" (MANCHESTER OPERATION) FOR PROLAPSE OF THE UTERUS

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IN JUNE, 1932,<sup>1</sup> I first called attention to the satisfactory results obtained by the so-called Manchester operation for prolapse, variously known as the Donald, Shaw, or Fothergill operation. Essentially the same technic has also been used by Halban.

Since this preliminary report, which dealt mainly with the comparative merits of various operations, 66 patients have been operated upon by me with this method, with uniformly good results. Not in a single instance has the prolapse recurred, but in a few of the earlier cases there was some return of the cystocele noted, which can be ascribed to insufficient closure of the pubocervical gap.

The operation has proved reliable, of wide applicability, readily taught to assistants, and gives surprisingly uniform results.

It appears to me that the description given by Shaw<sup>2</sup> is rather complicated and confusing, and that the various steps of the operation can be very simply and readily described if certain fundamental facts are understood and kept in mind.

## TECHNIC

In the lithotomy position, after due preparation and emptying of the bladder, the cervix is grasped and should readily be pulled down, at least, to just beyond the introitus of the vagina. If this requisite is present, the operation may be proceeded with after *thorough* dilatation of the cervical canal and curettage.

A triangular denudation, beginning approximately 2 inches below the urethra and carried in a straight line just lateral to each side of the portio, is made (Fig. 1, *A*). The cervix is then raised up toward the symphysis and the incisions united behind the cervix as shown in (Fig. 1, *B*).

Within this delimitation of the flap the vaginal mucosa is rapidly removed, laying bare the base of the bladder and the pubocervical tissues. This is done partly by sharp, partly by blunt dissection. The bladder is now pushed back in the mid-line, being freed from the cervix by a few snips of the scissors. This reflexion of the bladder further demarcates the lateral pubocervical fasciae or tissues (bladder pillars). Thereupon the bladder angles must be completely and fully freed from beneath the pubocervical tissues and pushed upward (Fig. 2, *A*).

The pubocervical tissues of each side are caught in a chromic suture and divided between portio and bladder as shown in Figs. 2, *B* and 3, *A*. This exposes the uterine vessels which are next tied at a level just above the site selected for transverse cervical amputation (Fig. 3, *A* and *B*).

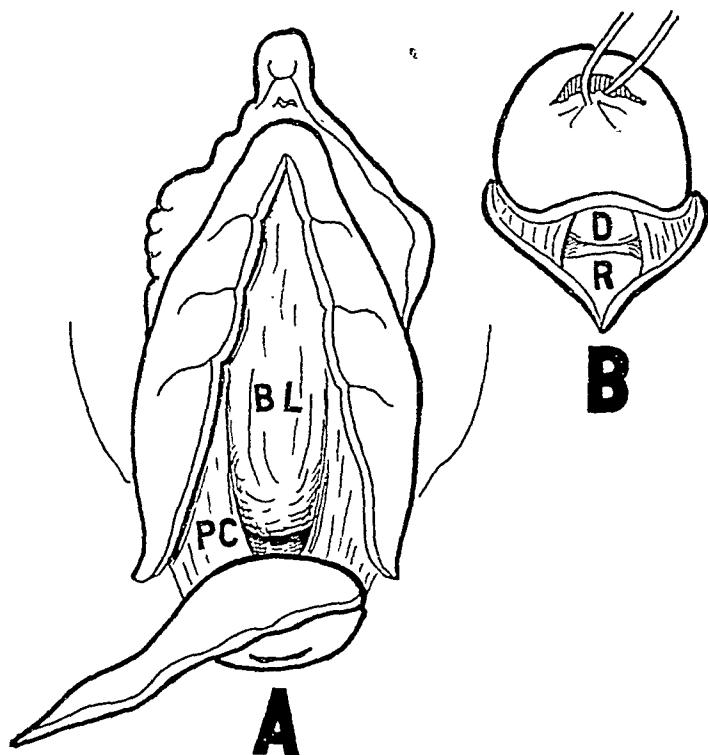


Fig. 1.—Triangular denudation from  $\frac{1}{2}$  inch below urethra, circumcising the cervix. A. Anterior view; *BL*, Bladder separated from cervix sufficiently to show the tenous areolar tissue between cervix and bladder; *PC*, pubocervical tissues (bladder pillars) anterior to bladder. B. Cervix pulled upward showing posterior part of denudation; *D*, Douglas' culdesac; and *R*, Rectum. To either side of these structures the sacro-uterine ligaments and posterior portion of the parametria are exposed.

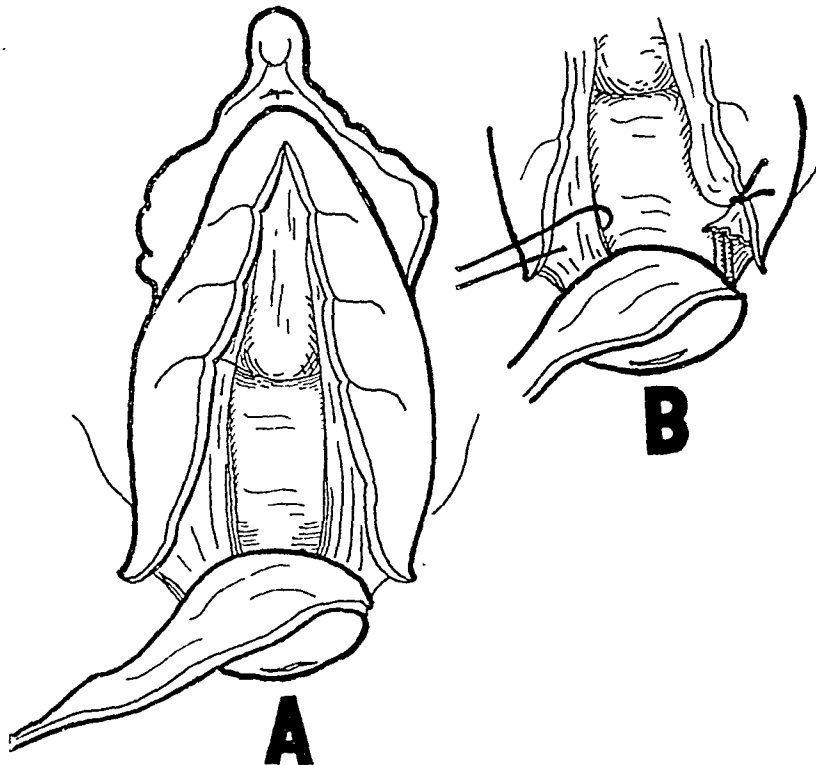


Fig. 2.—A, Bladder elevated after separation from cervix and lower uterine segment. Further demarcation of the pubocervical tissues. B, United suture (left) through pubocervical tissue (bladder pillar). To right, suture has been tied; bladder pillar cut, exposing the uterine vessels.



The flap posteriorly is readily reflected downward from the cervix from 2 to 3 inches by blunt dissection, and, if the culdesac is low, the peritoneal reflexion is likewise mobilized and pushed away or not infrequently either advertently or inadvertently opened. If thus opened, the enterocele sac should be completely mobilized

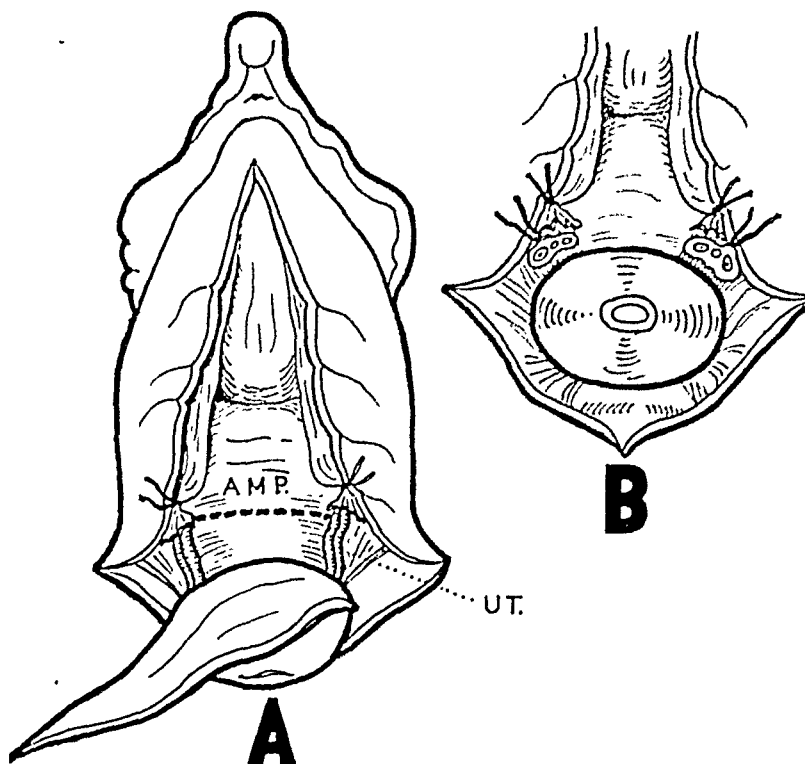


Fig. 3.—A, Both bladder pillars tied and cut, exposing uterine vessels; *A M P.*, above broken line which shows line of amputation; *U T.*, left uterine vessels. B, Upper tied sutures on bladder pillars; lower on uterine vascular bundles. Cervix amputated in slightly conical form. Lateral to and below the cervical stump the exposed parametria are seen.

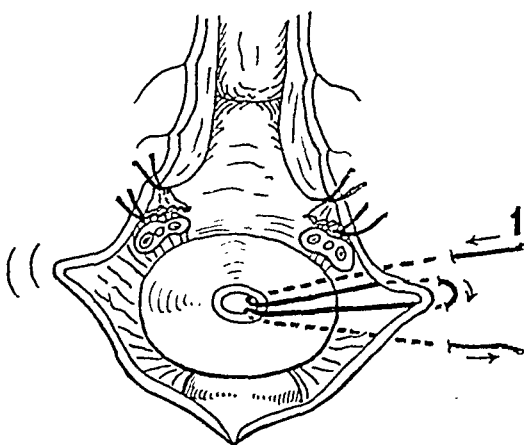


Fig. 4.

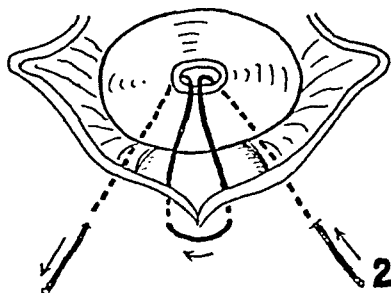


Fig. 5.

Fig. 4.—The first deep suture placed but not tied (1). This suture enters and leaves the cervix in a buried fashion but intermediately the edge of the mucous membrane is grasped. A similar suture is to be placed on the patient's right.

Fig. 5.—The posterior suture (2) which includes both sacrouterine ligaments, in principle is exactly similar to suture 1.

and closed by a purse-string suture placed high and including the posterior surface of the uterus. The cervix is then rapidly amputated flat or by a slight cone-shaped section (Fig. 3, B).

After hemostasis, the entire large gap resulting from the denudation and amputation is readily closed by 4 sutures.

The first sutures to be placed are the lateral ones, which enter the mucosa of the lateral fornix at least 1 or 0.5 inch from the edge, penetrate the base of the parametrium and enter through the substance of the cervix to appear in the cervical canal (Fig. 4). The suture then returns superficially, grasps the mucous membrane close to its edge, re-enters the cervical canal and retraverses the tissues in a reverse

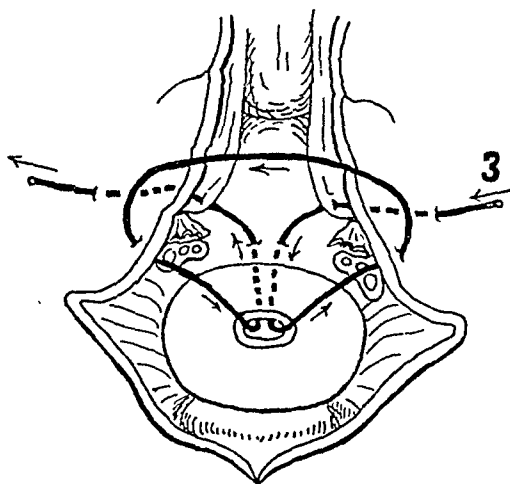


Fig. 6.

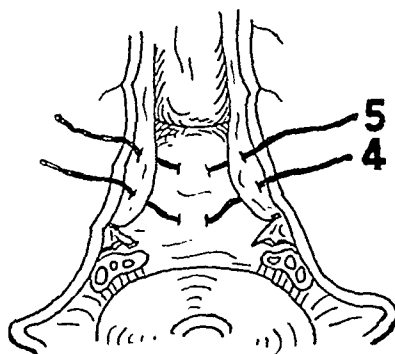


Fig. 7.

Fig. 6.—Anterior suture (3). This suture includes not only the mucosa but also the bladder pillars (immediately above the site at which they were tied in Fig. 3, B). It is important that the suture enter and leave the cervix close to the median line.

Fig. 7.—Sutures 4 and 5 are placed after suture 3 is inserted, but before 3 is tied. Sutures 4 and 5 further obviate the likelihood of descent of the bladder.

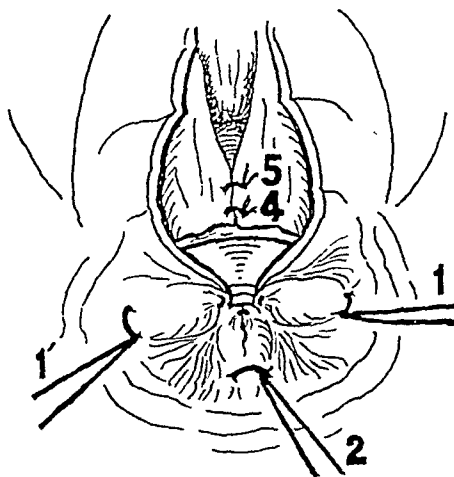


Fig. 8.—Suture 1, 1', and 2 have been tied. Suture 3 has been placed but omitted from the diagram to avoid confusion. After 1, 1', and 2 have been tied, 4 and 5 are next tied before the final cervical suture 3 is tied. The rest of the gap in the pubo-cervical tissues and in the anterior vaginal mucosa are then closed in turn by interrupted stitches. To avoid confusion suture 3 is not shown.

fashion, ending about 1 inch below the beginning of the suture (Fig. 4). A similar suture is placed on the opposite side.

Next an identical type of suture is passed through the posterior fornix. This suture, as shown in Fig. 5, takes in the posterior portion of the parametrium and insertion of the sacrouterine ligaments.

The last suture to be placed is the anterior one, which begins on the patient's left side, well above and lateral to the cervical stump. The mucous membrane is

pierced at least 1 inch from its edge. The suture then passes through the severed portion of the pubocervical tissues and penetrates the cervix close to the median line, appearing through the canal. It next passes through the vaginal mucous membrane close to its edge on the same side at which it was started, then through the mucosa close to the edge on the opposite (right side), re-enters the cervical canal, comes out of the cervical tissue close to the midline, takes in the pubocervical tissues of the right side, and ends on the right by penetrating the mucous membrane of the vagina 1 inch from its edge (Fig. 6).

When these sutures are tied, the cervix is entirely covered by mucous membrane. When there is a large cystocele, a few intermediate sutures should approximate the pubocervical tissues to the anterior wall of the uterus (Fig. 7, sutures 4 and 5). The gap between the cervix and urethra has been greatly lessened in length and a few deep intermediate sutures, which take in the pubocervical tissues, fully obliterate the residual space and prevent the bladder from descending (Fig. 8). The mucous membrane is then closed. A strip of selvaged iodoform gauze is carried into the cervical canal and the operation is completed by means of a thorough posterior colporrhaphy.

### RESULTS

The results in 67 cases, all of which have been very carefully watched since they were operated upon, have been surprisingly good and uniform. In not a single instance has there been any descent of the cervix, which appears firmly but not too rigidly fixed in a high position. The fundus of the uterus appears to be anterior to the transverse midplane and in most instances the fundus is found in ante-flexion. Because of the high position of the cervix, the resultant anterior vaginal repair has been surprisingly satisfactory, as the success of this largely depends on two fixed points, the subsymphyseal tissues and an undescending cervix.

I have employed the operation on my service and in my private practice regularly where descensus, whether of first, second, or third degree has required treatment (30 cases of first degree prolapse, 25 of second degree, 11 cases of third degree). Even in the most extreme degrees of prolapse, with the fundus projecting far beyond the introitus, the operation was used. In one instance, prolapse of the cervical stump after supravaginal abdominal hysterectomy, was likewise treated by means of the same technic, with success.

In two cases, the anterior fornix was opened and the tubes ligated before the amputation was performed. In one instance, multiple vaginal myomectomy was first performed.

### RATIONALE OF THE OPERATION

What is the *modus operandi* of the operation? Mechanically the amount of shortening obtained by amputation of the cervix and passage of the sutures through the base of the parametria, in many instances alone does not account for the resulting fixation of the cervical tissues. It appears to me that the favorable result is obtained by condensation and shrinkage of the parametrial elastic and connec-

tive tissues due to the aseptic trauma occasioned by the operation, and resembling to some degree the fixation noted after infection of the parametria. The sole difference is that the scars obtained by operation are resilient and entirely painless while the opposite results after inflammation.

The morbidity following the operation has been remarkably slight; the mortality so far nil. In 2 of the earlier cases insufficient flaps were fashioned and consequently part of the cervical tissue was left bare after the sutures had cut through. In spite of this the final result was perfect. The result of the anterior repair depends upon the care taken in exposing and suturing the pubocervical tissues and also upon the strength of these variable structures, as the cervix remains well fixed high in midpelvis. In no instance has dysmenorrhea or stenosis of the cervix developed. One patient became pregnant a few weeks after the operation had been performed, and abortion by means of x-ray was induced. We feel that in younger patients who have sufficiently large families, ligation of the tubes is indicated during the operation, that if pregnancy is to supervene, the operation should be postponed, although the Manchester School has reported successful pregnancy and delivery.

All in all this operation fulfills the requirement of a readily learned operative technic, applicable in a wide range of conditions; comparatively easy execution with low morbidity and mortality, and with excellent and uniform results. In our hands it has proved more satisfactory and more readily carried out than vaginal hysterectomy. It avoids incision of the abdominal wall and ventrofixation, which too often is attended by stormy convalescence and frequently followed by the development of ventral hernia.

#### REFERENCES

- (1) *Frank, R. T.*: AM. J. OBST. & GYN. 24: 574, 1932. (2) *Shaw, W. F.*: AM. J. OBST. & GYN. 26: 667, 1933.

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*Addendum.*—In the nine months which have elapsed since handing in this manuscript, 40 additional cases have been operated upon. These consist of 30 cases of first degree prolapse, 5 of second, 3 of third degree, and 2 of prolapsed cervix after supravaginal hysterectomy. This brings the total to 106 cases distributed as follows:

First degree	60 cases
Second degree	30 cases
Third degree	14 cases
Prolapse of cervix stump	3 cases

There has been one recurrence of prolapse in an asthenic, underweight patient, who should not have been subjected to operation. The recurrence was noted within the second month following operation.

# CORRELATION OF THE UTERINE AND OVARIAN CYCLES

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IT IS possible to trace, even in our modern sophisticated scientific literature, something of the older idea that man was somehow set apart from the other mammals physiologically as well as mentally, though the echo becomes fainter and fainter as comparisons between the two groups become more careful and exacting. Since man is available for scientific experimentation to a very limited extent indeed, it is fortunate that these comparisons yield such valuable results. An understanding of the interrelations of the sex organs in man is largely dependent upon a knowledge of these relations in the lower mammals. Reproduction is as fundamental as digestion and respiration, and the processes governing it are as much alike in different species as are other physiologic processes. In the course of evolution of a large group like the mammalia, it is to be expected that variations will be introduced, but such variations are generally of a minor character, the fundamental characteristics being only slightly modified, particularly with physiologic processes.

The classic research of Hitschmann and Adler gave us our first view of the remarkable changes taking place in the uterus in regular recurrent cycles of about twenty-eight days, but it has been due to the ease with which these changes may be studied in laboratory animals that a working knowledge of them and associated changes in the ovary has been obtainable. There is a considerable body of literature on the interrelations of the uterus and ovary, covering many forms, from rodents and marsupials to the monkey and man, all of which indicate a close similarity in the essentials of these cycles in the entire group. These similarities will be pointed out in the following paragraphs.

## CYCLES IN THE CAT

In the cat two distinct types of cycles may be distinguished, affecting both the uterus and ovary, first, those which are accompanied by ovulation and corpora formation, and second, cycles in which the mature follicles become atretic without ovulation. These types will be described quite fully, as the typical ones for mammals generally.

*With Ovulation.*—The cycles in the cat average about seventy-five days in length, though the cycle in the vagina may be of any length from a few days to two months (Evans and Swezy, 1931a). During the middle of these periods in the non-pregnant animal, the ovary contains many growing follicles of a small to medium

size, with corpora showing early stages of regression. The uterus at this time is in the so-called resting phase, and is more slender and threadlike than at any other time of the cycle, cross-sections showing a very low endometrium. The glands of the uterus are short and straight and the cells lining them are low cuboidal in shape. Between this time and estrum, or the ovulation period, a considerable amount of growth takes place, in which the glands become longer and more or less coiled. This time of active growth shows many mitotic cells in the lining of the glands and elsewhere, and is more rapid in the two or three days preceding ovulation than during the earlier anestrus period. At the time of ovulation the endometrium has increased four or five times in thickness.

With the formation of the corpora after ovulation, definite changes occur in the glands of the uterus. The cells lining them become large, cylindrically shaped, and take on the appearance of secretion cells. The glands themselves increase still further in length, becoming coiled, giving a cross-section of the enlarged uterus the characteristic spongy appearance known as progestational proliferation. This phase of uterine development may be designated as the secretion phase, and lasts as long as the corpora are actively functioning, after which regression takes place, this extensive new growth of tissue breaking down and being resolved. The beginning of regression in the uterus may be noted before the corpus shows evidences of degeneration. The regressive changes are completed some time near the middle of the cycle, the uterus returning to the small size of the resting phase. This resting stage seems to be a very short one, the new growth phase soon being evident in the few scattering mitoses in the cellular lining of the glands.

*Without Ovulation.*—It has long been considered that ovulation takes place in the cat only after copulation, but recent work of Evans and Swezy (1931b) has shown that ovulation occurs almost as frequently without copulation as does degeneration of the mature follicles. In the case of cycles in which ovulation does not occur, there are no evidences that they are materially altered in length or in the changes that normally precede ovulation, the only differences noted being found after this period. There are the same growth phases in the uterus preceding ovulation, lasting until the first signs of atresia appear in the mature follicles, when growth ceases and regressive changes appear in the uterus. These degenerative changes take place without the extensive uterine development found after the formation of a corpus, the uterus presenting the structural characteristics of the ovulation period. The uterus in the nonovulating cycle thus lacks the secretion phase found in the ovulating cycle.

There seems to be a longer resting phase in the uterus in these nonovulating cycles than in those accompanied by ovulation, regressive changes occurring earlier, but the new growth beginning at about the same time as in the ovulating cycles. The presence or absence of a corpus seems to have little or no effect on the early growth of follicles, hence on the length of the cycles.

#### CYCLES IN OTHER MAMMALS

The cyclic changes in the uterus and ovary in the rat and mouse are less satisfactory for comparative purposes than are those of most other mammals which have been described. Their cycles are shortened, particularly in the phase following ovulation, regression beginning almost immediately, without further uterine development. The phases preceding ovulation are similar to those in the cat, growth beginning before proestrus and reaching its greatest expression at estrus. The corpus

of these short cycles seems to differ physiologically from those of the cat or other mammals with a longer cycle, as may be seen in its inability to induce the secretion phase in the uterus.

In the guinea pig the same phases of growth precede ovulation, with certain definite changes following it (Loeb, 1911). The longer cycle, sixteen days, makes these changes as clear-cut as in the cat, though without the same type of progestational proliferation. It is in the larger mammals, however, that these cyclical phases, especially the complex structure of the endometrium associated with the corpus in the ovary, reach their most striking development; complex structures which are comparable in every way with those in the primates, hence of great importance in attempting to understand the cyclical phases of the human cycle. A summary of the most important of these is given in Table I.

TABLE I. SUMMARY OF DATA ON UTERINE CYCLES OF DIFFERENT MAMMALS

ANIMAL	ANESTRUM	ESTRUM OR OVULATION	METESTRUM	AUTHOR
Cat*	Low endometrium with short and simple glands	Increase 3x, glands long, coiled	Complex secretion phase	
Dog	Very low endometrium, short, simple glands	Increased 5x, glands long, slightly coiled	Complex secretion phase	Evans and Cole (1931)
Ferret	Small, short, simple glands	Increased 3x, glands long and coiled	Complex secretion phase	Hill and Parkes (1933)
Gray squirrel	Small, shrunken, short glands	Increased 2.5x, glands coiled	Complex secretion phase	Deanesly and Parkes (1933)
Sow	Endometrium low, simple glands	Increase in thickness and length of glands	Complex secretion phase	Corner (1921)
Rabbit†	Endometrium low, short glands	Increase 5x, glands coiled	Complex secretion phase	Hammond and Marshall (1925) Original
Monkey‡	Low endometrium, short, simple glands	Increase 5x, glands coiled	Complex secretion phase	Corner (1923)
Man	Low endometrium, glands short and simple	Increase 3x, glands long and coiled	Complex secretion phase	Schroeder (1930)

\*In the nonovulating cycles the secretion phase is not present.

†This is true for the first heat period after anestrus. If mating is not allowed and ovulation does not occur, a series of heat periods follow, with only slight regressive changes in the uterus between them.

‡May also have nonovulating cycles like the cat.

A comparison of photographs of the uteri of these animals with those of the cat at corresponding phases of the cycle, shows that the type and relative amount of change are precisely similar. In fact, in most cases, pictures of one might be interchanged with those of another. The relative increase in thickness of the endometrium at estrus, hence the amount of growth, varies but little in the entire group.

#### CYCLES IN THE PRIMATES

A great amount of work has been done on the uterine and ovarian cycles in the primates, both in the monkey and in man, but, so far, the relations between these two cycles have not been stressed as much

as have the relations between them and the menstrual cycle. This has not clarified the situation, largely due to the fact that most investigators have taken the menstrual cycle as the starting point and the regulator of the other cycles and their periodicity. The course of evolution of the reproductive processes in the mammals shows clearly that the ovarian and uterine cycles are the primary ones, menstruation having been added on, so to speak, in the higher groups. In any consideration of these interrelations this must not be forgotten. It has been shown, by a number of clinicians and investigators, that normal ovarian and uterine functions may be carried on without menstruation, including successful pregnancy, both in the monkey and in man. This would imply that menstruation may not be as fundamental as many have considered it. The fact that disturbances of the menstrual periods often indicate serious disorders, apparently means that they may be indicators of normal hormonal and physiologic relations, without being themselves the important regulating factor.

It is apparent, in reviewing what has been reported on the relations between the ovarian and uterine cycles, that the condition of the uterus affords a very accurate criterion for the stage of the cycles in the ovary, more accurate than that of the ovary itself, as in cases where ovulation does not occur. This has been pointed out by Evans and Swezy (1931a). Thus, for example, there are no known instances of ovulation normally taking place with the uterus showing either the resting condition of anestrus or the secretion phase of the later part of the cycle. In like manner, the occurrence of the typical estrous growth in the uterus is good evidence that the ovary contains mature follicles ready to ovulate. Since this is true in all of the lower mammals, so far as present data can prove, we must accept it as true in the primates also, until definite evidence to the contrary is brought forth, as all of the evidence at the present time agrees in showing their fundamental similarity to the other mammals.

*Cycles in the Monkey.*—Heape (1894) and Van Herwerden (1906) were the first to study the uterine cycle in the monkey, including the relation of menstruation to ovulation. Much has been done since that time, notably by Allen (1927), Corner (1923), and Hartman (1932). For the purposes of this review, the work of Corner offers the most valuable material, since he gives detailed notes and photographs of the uteri and ovaries of a number of monkeys at different phases of the cycle. These will be described, not in the sequence in which Corner places them, but in the sequence suggested by a close comparison with the cat and other animals.

During the middle of the ovarian and uterine cycles the uterus is small and shrunken in size, the endometrium low with short simple glands, greatly resembling that of the cat. A number of excellent photographs are given showing stages of the growth of the uterus from this time up to the ovulation period, with corresponding growth in size in the follicles in the ovary. This growth, like that of the cat, results in a thickening of the endometrium and the elongation and coiling of the glands, producing an estrous or ovulation picture which is identical, in all



essential details, with that of the cat and dog at estrum. Following ovulation and the formation of the corpora, the elaborate progestational proliferation is produced, with its regression in a short time. Comparisons of these stages with those of the cat and dog leave no doubt that the processes, hence the harmonic relations, are similar in the two groups.

It has been well established that ovulation may not occur in some cycles. Van Herwerden (1906) noted that the endometrium in such cases did not show the extensive development found with a corpus. Later investigators have not fully described the uterus in these cases, but Van Herwerden's observations would indicate a condition similar to that in the nonovulating cycles in the cat, the uterus regressing without the formation of progestational proliferation. When the ovulation period has passed without ovulation in the monkey, the uterus probably regresses when the mature follicle becomes atretic.

*Cycles in Man.*—The amount of work done on the human sex organs is too voluminous to even touch upon here. The work of Schroeder (1930) stands foremost in describing the uterine cycles. He gives excellent photographs of the uterus at different stages of its development. He recognized eight types of uterine changes, the beginning of proliferation or growth, the middle of proliferation, and the end of proliferation being comparable to those from anestrus to estrus in the lower mammals. The end of proliferation is the ovulation period, followed immediately by the beginning, middle, and end of secretion, phases associated with a functional corpus, metestrus in the lower mammals. Desquamation and regeneration are comparable to the regression and resting periods in the cat and dog. The cases he describes under these headings, with the day of the menstrual cycle at which they occurred, are shown in Table II.

Near the middle of the uterine-ovarian cycle, corresponding to anestrus in the lower mammals, the uterus is smaller than at other periods, with low endometrium and short simple glands. Between this time and the ovulation period a relatively great amount of growth takes place, the endometrium increasing about three times in thickness, with elongation and coiling of the glands. This is the same process already described for the cat. Following ovulation and the formation of the corpus, growth changes proceed rapidly, resulting in the secretion phase, with characteristic cheeselike progestational proliferation of great complexity and thickness. Regression of the endometrium begins with the earliest regression of the corpus, and is rather rapid, as would be expected from the amount of tissue to be removed, and seems to be completed near the middle of the cycle. These phases of the uterine-ovarian cycle cannot be definitely allocated as periods of the menstrual cycle, since they occur at all stages of the latter, as is so well shown in Schroeder's table (Table II).

Evidences have been produced by a number of clinicians showing that, like the monkey, ovulation may not always take place, with a resulting lack of corpora in the ovary and the secretion phase in the uterus. It seems probable that the cycle in these cases is similar to the non-ovulating cycle in the cat.\*

#### DISCUSSION

In describing the uterine changes in the different mammals no attempt has been made to point out the differences that exist between

\*Mazer and Goldstein (*Clinical Endocrinology of the Female*) found that a fair percentage of their cases showed a lack of progestational proliferation in the uterus in the two or three days preceding menstruation. This, they consider, means a lack of ovarian function and, apparently, is an indicator of the need of hormone therapy, a conclusion which is unjustifiable.

TABLE II—DATA ON TYPE OF ENDOMETRIUM FOUND IN 898 HUMAN CASES GIVEN BY SCHROEDER (1930), AND OCCURRENCE OF FOLLICLES IN HUMAN OVARIES FROM NEWELL, ET AL. (1930), AND PAPANICOLAOU (1933)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Endometrium																												
Beginning of proliferation.....	1	1	2	5	8	11	17	6	9	7	6	5	5	3	2	2	2	...	2	1	1	2	...	3	...	1	...	...
Middle of proliferation.....			1	3	8	10	13	24	30	38	24	8	5	5	5	1	2	...	1	1	...	2	1	2	...	...	...	...
End of proliferation.....					2	1	1	9	1	9	12	25	19	22	11	16	6	10	1	4	4	4	3	3	...	...	...	...
Beginning of secretion.....								...	1	1	...	...	1	3	4	4	6	4	26	29	13	6	6	5	2	5	4	...
Middle of secretion.....												...	...	...	...	...	2	...	1	15	18	17	23	14	9	4	3	8
End of secretion.....	2	3	1	3	3	3	1	...	1	1	1	...	...	...	1	...	2	...	1	2	2	3	4	8	19	7	2	12
Desquamation.....				3	1	1	2	...	1	...	...	...	1	...	...	...	...	...	...	...	...	1	...	1	...	...	1	4
Regeneration.....													1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	1
Size of follicles																												
Small, up to 6 mm.....					1	...				1	...	1	1	...	...	...	1	...	...	...	...	3	...	...	...	...	...	...
Medium, 7 mm. to 9 mm.....		1	...		1	...	1					1	...	3	1	2	...	...	...	1	1	...	1	...	...	...	1	...
Ovulation size, 10 mm. plus.....		1	...				1	1	1	3	2	4	5	3	1	2	1	...	...	...	...	...	1	...	1	2	...	1

them. The essential features of this cycle, as we understand them, may be summed up briefly; from a resting or quiescent condition of very brief duration near the middle of the cycle, a period of growth takes place which lasts until the time of ovulation. If the follicles ovulate and corpora are formed, the secretions of the latter induce further complex growth in the uterus, followed by regression of both structures, beginning at about the same time. If no ovulation occurs, regression of the endometrium begins soon after the ovulation period has passed, coincident with atresia of the mature follicles. These are fundamental processes, and, so far as present available data can prove, are exactly similar in all of the animals so far studied, from the rat and guinea pig up to man. Each species seems to have in this, as in all other characteristics, minor variations which set it apart from all other species, yet the essentials do not seem to vary. The period when a mature follicle is ready to burst, finds that a certain amount of growth has taken place in the endometrium. This seems to be invariable and to depend on the fact that mature follicles are associated with folliculin, the stimulus for endometrial growth. The presence of a functional corpus also means a certain type of development beyond this initial growth phase, except in the rat, which lacks the secretion phase. It has been well established by a number of investigators that the cycles in the uterus are dependent on the cyclical production of hormones by the follicles and corpora in the ovary, and, since the relations between the follicles, ovulation, and corpus formation are the same in the primates as in the lower mammals, it is to be expected that the course of events will be fundamentally the same in man as in the cat and dog and even the guinea pig.

Much work by many investigators has established the validity of these relations between the phases in the uterus and those in the ovary, and the remarkable regularity of their recurrence. The value of these facts lies especially in the application that may be made of them in determining the phase of the cycle in the primates by an examination of the uterus. The importance of this for determining that much discussed question, the time of ovulation in man, is at once apparent. A study of Table II shows how this may be utilized. The appearance of uteri with endometria in the beginning of the secretion phase, at times ranging from day eight to day twenty-eight, *means, beyond a doubt, that these days were immediately preceded by ovulation, since this phase of uterine development is produced normally only by a new corpus.* No other explanation seems possible. The end of proliferation, ranging from day five to day twenty-seven, also means that ovulation was imminent throughout that time, since this phase in the uterus has been found occurring only when mature follicles were present in the ovary.

The 11 monkeys figured by Corner may also be tabulated in the same way. These are too few to cover the entire cycle, but the presence of

a middle proliferation type of uterus at day nineteen seems fairly certain evidence that the ovulation period would come a few days after this date (Table III). Also the beginning of proliferation at day twelve could only mean that ovulation would come near the latter part of the cycle.

TABLE III. DATA ON THE MONKEY: UTERUS FROM CORNER (1923) AND OVULATION FROM CORNER, ALLEN (1927), AND HARTMAN (1932)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Uterus																				
Beginning of proliferation				2								1								
Middle of proliferation										1							1		1	
End of proliferation													1							
Beginning of secretion																	1			
Middle of secretion																	1			
End of secretion	1			1																
Ovulation			1						2	8	2	4	3	3	6	3				

Much stress has been placed on the finding of tubal eggs as the decisive test for ovulation, yet, when the number of these is compared with the number of cases examined during the middle of the cycle, with not only *no evidences of ovulation, but with the uterus and ovary in the anestrus or resting phases*, it is evident that this test is inadequate, though good as far as it goes. There should be some criterion by which to judge the phase of the cycle of any animal. This may be done with great accuracy in the lower mammals by an examination of the uterus. There seems to be no possibility of mistaking growth in the endometrium before ovulation or the secretion phase following it. All of the work available at the present time shows no single instance of a lack of this correlation in the normal animal. The primate cycles are fundamentally similar to those of the lower mammals, and should be judged by the same rules. For these reasons a criterion by which to judge the time of ovulation would be the amount of growth present in the endometrium. Evidences of regression are also unmistakable, and definitely mark certain phases of the uterine and ovarian cycles.

Allen et al. (1930) measured the follicles in 36 human ovaries, and Papanicolaou (1933) examined 16, noting the follicles as small, medium, and large. When the results of these observations are tabulated (Table II), it is found that the distribution of follicles through the menstrual cycle closely parallels the distribution of the corresponding phases of the uterus. Follicles of ovulation size occur at days ranging from the second to the twenty-eighth day of the cycle. Medium sized follicles are found from the second to the twenty-fifth day. That some of these follicles of ovulation size were atretic suggests the occurrence of a non-ovulating cycle, such as occurs in the cat.

The number of monkeys with known ovulation dates is small, yet, when these are tabulated (Table III), they are found to have a distribu-

tion similar to that of the mature follicles and the uterine phase associated with ovulation in the human cases. They also definitely show that ovulation in the monkey is not confined to the twelfth to fifteenth days of the menstrual cycle, the period given by most writers as the ovulation days in the primates. When these tables, representing the most careful work in this field up to date, are studied, it is found that the majority of ovulations occur between day ten and day eighteen, with a smaller number occurring at other days, as early as day three in the monkey and as late as day twenty-eight in man. It must be noted, however, that the majority of cases were examined during the middle of the cycle, with only a scanty number during the early and late days.

The record of events preceding and following ovulation is indelibly stamped upon the uterus, and a study of its condition should enable us to place the time of ovulation in the menstrual cycle of the individual within two or three days. Hartman's data indicate striking regularity in the occurrence of ovulations in successive cycles in individual monkeys, each having a rhythm peculiar to itself. Menstrual cycles in captive monkeys are notoriously irregular, apparently differing in this respect from the uterine-ovarian cycles. The regularity of the latter, their rhythms being dependent upon the reactions between ovarian and pituitary hormones, is well known in most of the lower mammals and is to be expected in the human cycles (Swezy, 1933b).

#### SUMMARY

Two types of cycles occur in the cat, one, with ovulation, and two, with no ovulation. In the latter cycles the secretion phase does not occur in the uterus, the endometrium regressing with atresia of the mature follicles. These types are similar to those found throughout mammals generally. The close correlation between these phases and the phases of the ovary gives us a criterion by which to judge the time of ovulation in the primates by the condition of the uterus.

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## SPLIT PELVIS IN PREGNANCY\*

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I G., A PRIMIPARA, aged twenty-eight, Italian, entered the Antepartum Clinic of the New York Polyclinic Hospital on June 16, 1932, approximately twenty-four weeks pregnant. Her antepartum course was nontoxic throughout.

Past history showed no trouble in walking or exercising. There was no history of trauma. There were no urinary symptoms. She did not know that there was anything structurally wrong with her.

Menstruation began at fourteen, periodicity was normal, twenty-eight-day cycle, lasting three or four days with comenstrual pain. The last period was Dec. 5, 1931.

Physical examination was normal except for the abdomen and pelvis. The umbilicus was situated very low in the midline. The iliac crests flared outward



Fig. 1.—Abdomen. Note low position of umbilicus. Operative scar present. Iliac crests outlined in ink.

(Fig. 1). The urethra was normally situated. The clitoris was prominent. The vagina was foreshortened from above down and widened transversely. The labia majora were widely separated anteriorly. There was almost no perineal body.

Pelvic examination disclosed no symphysis pubis. A narrow, fibrous band occupied the position of the symphysis. X-ray examination showed absence of the symphysis with 11 cm. separation. The pelvic bones were poorly developed, and the ilia directed more outward than usual. Internal measurements were ample (Fig. 2).

Labor was expected on the twelfth of September, 1932, but began three days earlier. The membranes ruptured one-half hour after the onset of labor. Presentation was a vertex, and the head was in the pelvis. Labor was active. The cervix dilated to three fingers in fifteen hours, and morphine and scopolamine followed by rectal ether was given. Nine hours later there was no further progress. The cervix

\*Presented before the New York Academy of Medicine May, 1933.

was far anterior, not effaced, its anterior lip being very short and its posterior lip being about 6 inches long.

Laparotrachelotomy was done under ether anesthesia. A retention catheter was left in the bladder. Due to the position of the umbilicus, incision was to the right of the midline. Upon incising the fascia from above down, abnormal bleeding was encountered, so the peritoneum was opened at the upper angle of the incision and the superficial layer of the fascia carefully dissected. This revealed, in the lower half of the wound, a mass of fibrous and muscle tissue which looked like bladder wall. The catheter was felt in this tissue. Poupart's ligaments were fused in the midline with a mass of heavy, dense, fibrous tissue composed of aponeurosis, rectus sheath, and incorporating the bladder. This tissue was dissected off to the right, and the operation completed in the usual manner. Closure was by means of 3 strings of dermal suture without retention sutures. Postoperative course was uneventful.



Fig. 2.—X-ray picture of pelvis, showing absence of symphysis pubis.

and afebrile. The baby weighed 6 pounds 6½ ounces. The patient and baby left the hospital in good condition on the fourteenth day.

This woman had an ample pelvis and normal labor was anticipated. However, after twenty-seven and one-half hours there had been insufficient progress for twelve hours. Dystocia was due to a distorted mechanism of labor. Thus, there was no anterior fulcrum, and the uterine contractions exerted as much force in the direction of the abdominal wall as they did in the axis of the birth canal. The low lying sacral promontory contributed to deflecting the head anteriorly instead of down. The cervix was thus shortened anteriorly and elongated posteriorly. The head did not descend; progressive dilatation of the cervix did not take place, and effacement was absent. For these reasons cesarean section was done. The abdominal route was chosen as version or difficult forceps was contraindicated because of lack of cervical effacement and the probable danger of rupturing the fibrous band joining the pelvis in front.

Laparotrachelotomy was selected as the membranes had been ruptured many hours and repeated vaginal examinations had been made. It was consequently felt that the flap operation was safer, even though some difficulty with the bladder might be encountered.

This appears to be the first case of split pelvis without exstrophy of the bladder. The abnormal location of the bladder beneath the skin in the fascia is testimony that embryologically there was an arrest of development of the anterior abdominal wall, although this arrest was not so extensive as to cause a lack of fusion and an actual exstrophy.

Since this case was reported the patient has gone through her second pregnancy. This was terminated by elective low classical cesarean section April 11, 1934, under local anesthesia. The mother and baby left the hospital in good condition April 25, 1934.

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Kraul, Ludwig: Clinical and Pathological Observations in "Chocolate Cysts" and Hematomas of the Tubes, Ztschr. f. Geburtsh. u. Gynäk. 106: 64, 1933.

Twenty cases of chocolate cysts and 21 cases of hematosalpinx were analyzed clinically and in regard to their histogenesis. Serial sections of all 20 chocolate cysts revealed aberrant endometrial tissue in only 5 instances. The other 15 cysts differed grossly in nothing from those containing endometrial tissue. Four were follicular cysts, two contained corpus luteum cells. A myomatous uterus was associated with the process in 6 cases. In 3 others only old inflammatory changes of ovaries and tubes were found. In all five cases of endometrial cysts, the patients had pain, but only one complained of dysmenorrhea. Three had menorrhagias, 2 metrorrhagias.

Only 7 of the total of 20 chocolate cysts were free of pain; 13 suffered from dysmenorrhea.

Of the 21 cases of hematosalpinx 8 were associated with an ectopic pregnancy of the other side. The tubal mucosa of all of these was chronically inflamed. In 6 others, a fibroid uterus was found. All 21 women suffered from severe pains. Dysmenorrhea was present in a larger percentage than in those with chocolate cysts. The author concludes that the pathologic processes studied have no characteristic clinical symptomatology which could assure their diagnosis with any degree of probability. Their symptoms are identical with those of inflammatory adnexal processes.

GROVER LIESE



# SUPPURATIVE MASTITIS AS A COMPLICATION OF PREGNANCY AND THE PUERPERIUM

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**S**UPPURATIVE mastitis or breast abscess usually occurs as a complication of the early puerperium, although it is occasionally seen in the later stages of the nursing period and even during the course of pregnancy. The study of breast abscess has received very little attention in recent years, since the symptoms are so well known, the treatment so logical, and the outcome rarely serious. It seemed pertinent to us to reopen this topic and to review the instances of this complication occurring in a large series of women delivered on one service under comparative conditions. The results of this study comprise the following report:

*Incidence.*—From the opening of the Obstetrical Wards of the Johns Hopkins Hospital in 1896 to Jan. 1, 1934, there were 20,258 patients delivered at or near term and 113 of them developed suppurative mastitis, an incidence of 1 in 179 deliveries. On the other hand, Smith<sup>6</sup> has recently reported the much higher incidence of 1 in 58 deliveries among private patients. In the years preceding the establishment of routine postnatal clinics it seemed likely that many patients with mastitis were returning to the general surgeon; whereas after the introduction of these clinics almost all were being seen and treated by the obstetrician. This factor, however, does not entirely explain the difference in frequency between the private and the ward patients. We found 60 breast abscesses in 13,326 deliveries in the earlier group (1896 through 1924), an incidence of 1 in 222 deliveries; while in the more recent cases there were 63 in 6,932 deliveries, or 1 in 131. In private practice the physician is usually notified of any symptoms of breast abscess regardless of how late in lactation they develop; whereas the clinic type of patient might occasionally come to the attention of the surgical service. Yet it is incredible that only one-third of these patients should return to the service on which they were delivered.

In discussing puerperal infection, DeLee<sup>3</sup> states that "it is more common among the delicately bred well-to-do than among the poor, who, through ages of squalor and filth, have developed immunities which the others in their protected lives do not possess." Smith says that this factor would seem to be equally applicable to diseases of the breast. We are unable to concur with Smith's premise since there were only 2 cases of breast abscess in 840 private deliveries at the Johns Hopkins Hospital as compared with 111 cases occurring in 19,418 ward deliveries; an incidence of 1 in 175. Moreover, we cannot agree with DeLee's statement, since in our experience puerperal infection occurs far less frequently on the private service than in the general clinic population.

*Race and Parity.*—As Peckham<sup>4</sup> has shown, the Hopkins obstetric material is almost evenly divided between the black and white races and the number of primiparas

is in excess of multiparas by a ratio of 9 to 7. On analyzing the cases from this standpoint it was found that race played little or no part in the frequency of breast abscess, since there were 62 white patients (55 per cent) and 51 colored patients (45 per cent); a ratio of 1.21 to 1.

Increasing parity seems to be a relative safeguard against the development of breast abscess, there being 79 cases in primiparas, 20 in secundiparas, and 14 in greater multiparas. This confirms the experience of Winckel and Smith, who found that breast abscess was much more common in women nursing their first babies than in those who have previously suckled a child.

*Age.*—The age of the patient would be expected to conform to the normal range of the childbearing period, and since primiparas are more susceptible than multiparas, a preponderance of cases would be expected in the earlier childbearing years. Accordingly, the range is found to be from fifteen to thirty-eight years in the colored and from sixteen to thirty-nine years in the white patients, with a mean age of 22.12 years in the colored, and 22.56 years in the white; or 22.36 years for the entire group. These figures do not differ significantly from those of the general clinic population.

*Time of Appearance.*—The appearance of breast abscess with reference to time of delivery varied greatly. There were 7 cases in which suppuration developed and incision and drainage were necessary before delivery, thus leaving 106 more typical cases of postpartum abscess. Witcher<sup>8</sup> has shown that the antepartum cases do not differ from the more frequent puerperal type except in time of their appearance. A predisposition to the occurrence of mastitis during pregnancy is suggested by the work of Allen<sup>1</sup> who has shown that early in pregnancy the breast, and particularly the duct system, hypertrophies and with this its vascularity increases; while during the latter half of pregnancy there is an hypertrophy of the alveoli and a secretion of the epithelium lining these glandular structures. The same author has demonstrated that there is a definite cyclic development of the breasts, with increased vascularity associated with the menstrual cycle and this may aid in explaining the fact that of a total of 55 breast abscesses treated on the surgical service over a period of years, 25 (45 per cent) were not associated in any way with pregnancy. The cases of suppurative mastitis in newborn infants may also be explained on the basis of mammary activity stimulated in them by the hormones obtained from the mothers' milk.

The time of operation in the antepartum cases varied from thirteen weeks to two days before delivery, while in the puerperal cases operation was performed from one day to sixteen and one-half months after parturition, with an average of 29.29 days antepartum in the former group and 39.22 days postpartum in the puerperal group. However, 79 per cent of the latter occurred before the average period for the group with the majority of them developing in the third or fourth week postpartum. The most atypical case was that of a thirty-year-old white woman who, though she had had two previous full-term deliveries, nursed only the third child, and continued until symptoms of breast abscess developed at fourteen and one-half months.

The smallest number of days elapsing between a definite appearance of symptoms and operation was six, the greatest sixty, with an average of 10.82 days. In only one patient did symptoms develop antepartum (seven days) and operation took place postpartum (one day). Many cases were incised within seven days of the development of symptoms and 77 or 71.3 per cent of the total were operated upon within twelve days of their onset. Some of the remaining 31 cases probably would have been incised earlier had the patient presented herself sooner; the infection was deep-seated or diffuse in others and the time required to bring about localization and

fluctuation prolonged; and several had been treated as cases of simple mastitis with apparent success but which eventually showed suppuration and had to be incised and drained.

*Location.*—A point of considerable interest was the predilection of the infective process to localize in certain quadrants of the breast. In two cases, the breast in which the abscess occurred was not mentioned in the records, and in 5 others the abscess was bilateral. In the unilateral ones, 63 occurred in the right as compared with 43 in the left breast. The accompanying sketch gives the location of the abscesses according to the breast and the quadrant involved.

It may be noted that the most common points of infection were in the lateral hemispheres and particularly the inferolateral quadrants. Also it is significant that more abscesses occurred in the right breast than in the left. It seems probable from a study of these figures that trauma to the inferolateral quadrants of the pendulous and lactating breasts might be a very important etiologic factor and that location of the abscessed area in the right or in the left breast perhaps might be correlated with right- or left-handedness.

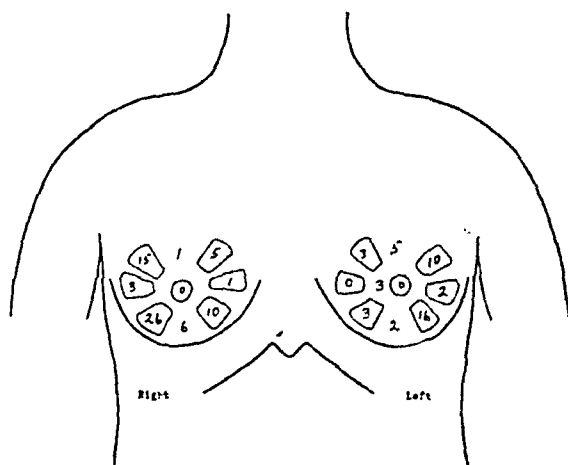


Fig. 1.—Schematic diagram of breasts showing areas where abscesses localized. Due to faulty records, the location of one in the right breast and four in the left could not be determined. Five cases were bilateral.

*Season.*—There is a seasonal variation in the incidence of breast abscess with an increased frequency during the winter and spring months, as is indicated by Table I. Twenty-nine cases, or 25.66 per cent of the total, were observed during the months of January and February. Whether one can correlate this finding with a similar variation in the prevalence of respiratory infection or whether it is merely coincidental cannot be proved, although we believe the figures adduced to be highly suggestive.

*Bacteriology.*—Although *Staphylococcus albus* is normally found in the milk and in the lactiferous ducts, Williams<sup>9</sup> was of the opinion that this organism was usually a harmless parasite and became pathogenic only after the tissues had been traumatized. He believed that most mammary abscesses develop after direct invasion by the causative organism through cracked nipples. Unfortunately in the earlier days of the Clinic, cultures from breast abscesses were not taken routinely so that a bacteriologic diagnosis is available in only 61 of the 113 cases.

Table II confirms the reports of Rubeska,<sup>5</sup> Smith and others, that *Staphylococcus aureus* is the most common causative organism in the development of breast abscess. The only sterile culture reported was obtained from a colored secundipara who developed symptoms of breast abscess seven days before delivery, had her right breast

incised and drained one day postpartum, and whose baby developed pemphigus early in life. It is possible that in this instance infection was due to one of the organisms found in pemphigus and which are difficult to grow on the ordinary culture media.

TABLE I. FREQUENCY OF BREAST ABSCESES ACCORDING TO PERIOD OF YEAR IN WHICH THEY OCCURRED

	NUMBER	PER CENT OF TOTAL
January to March	39	34.8
April to June	30	26.8
July to September	21	17.9
October to December	23	20.5
	113	100.0

TABLE II. CLASSIFICATION OF CAUSATIVE ORGANISMS

ORGANISM	NUMBER OF CASES
<i>Staphylococcus aureus</i>	40
<i>Staphylococcus albus</i>	7
<i>Staphylococcus aureus</i> and <i>albus</i>	1
<i>Staphylococcus</i> undifferentiated	2
<i>Streptococcus hemolyticus</i>	8
<i>Streptococcus</i> undifferentiated	2
Sterile	1
No culture report	52
Total	113

*Etiology.*—It is felt that the conditions listed below may well have played some rôle in the development of the subsequent infection in the breast. Certainly cracks or fissures in the nipples act as suitable portals of entry for the causative bacterial organisms. Trauma has been mentioned above. The association of breast abscesses with infection elsewhere in the body, such as the uterus, urinary tract, tooth, finger, or upper respiratory tract, occurs and culturally shows the same organisms too often to be merely coincidental.

TABLE III. ETIOLOGIC FACTORS ASSOCIATED WITH DEVELOPMENT OF BREAST ABSCESS

Simple mastitis (engorged breasts)	8
Cracked or fissured nipples	8
Trauma	6
Foci of infection	15
Infections from the nursing child	2

*Treatment and Prophylaxis.*—The routine care of the lactating breasts in the Clinic includes the use of 2 per cent boric acid solution to cleanse the nipples before and after each nursing. If cracks or fissures develop, the affected nipple is covered with a paste of bismuth subcarbonate and castor oil. This is removed before each nursing by washing with 70 per cent alcohol and boric acid solution. If the cracks bleed or the nipples become too tender to allow the infant to nurse directly, a nipple shield is used or the breast pump employed. Ice caps are used intermittently for painful lumps or diffuse engorgement. Only very rarely has it been found necessary to wean a baby because of the failure of fissured or cracked nipples to respond to treatment. If the fissure or crack does not heal, the breast is dried up by limiting the intake of fluids for twenty-four to forty-eight hours and applying ice caps. This is occasionally supplemented by purgation and less frequently by breast

supports or binders. Following the routine employment of this regime as first described by Storrs,<sup>7</sup> no mammary abscesses have developed while the patients were still in the hospital. Abscesses can usually be aborted if, with the first sign of beginning suppuration, ice caps are used and the breast placed at absolute rest; although occasionally, even if the condition is temporarily avoided, absorption is not complete and fluctuation will eventually develop and necessitate operative procedures.

Fluctuation once having developed, incision and drainage is almost the universally accepted treatment. Bier's method of hyperemia<sup>2</sup> for superficial abscesses has never been employed in this Clinic, though it may be of some value in selected cases. If the operator plans to cure the abscess in one operation, it is essential to break down all the honeycomb-like pus pockets. This requires the use of a general anesthetic. The skin incision is always made radial to the nipple or areola in order to avoid cutting across milk ducts. The incision may be enlarged by spreading a clamp. The gloved finger is the best instrument for breaking down all pus pockets. The abscess cavity should be tightly packed, preferably with vaseline gauze, and a firm breast binder applied for twelve to twenty-four hours in order to control bleeding from the subcutaneous vessels, since serious hemorrhages may occur when such precautions are not taken. Free drainage must be provided even at the expense of healthy superficial glandular tissue by making a stab wound through the healthy tissue at a more dependent area in the breast. Granulation must proceed from the base of the cavity or further incisions will be required before the abscess is finally cured. The tendency toward formation of walled-off pus pockets is indicated by the fact that it was found necessary in 30 cases to do 43 secondary operations; 3 being the greatest number of secondary operations on a single patient. In 9 cases the primary site had to be reopened because healing at the surface had become complete before the abscess cavity beneath had been obliterated, while in 21 cases it was necessary to incise new areas at the secondary operation.

Scrupulous cleanliness in the care of the nursing breast is essential for the prevention of suppurative mastitis. The value of digital stripping of the nipples and the application of medicines to the nipples during pregnancy to facilitate nursing and to avoid future cracks and fissures remains rather doubtful. It is debatable whether one breast should continue to function while the other is infected, and in some instances weaning the baby seems advisable. Since the inferolateral quadrants of the breasts are the parts most likely to be exposed to trauma from the motion of the patient's arms and are most often infected, the protection of these areas by supports or even pads throughout the period of lactation should be a prophylactic measure. Protection of the nipples from infection by the baby would seem important, since two patients in our series apparently developed breast abscesses from such a source. In one instance, the baby had a furuncle on the neck from which *Staphylococcus aureus* was cultured and a few days later the mother developed a mammary abscess due to the same organism. In the second case, the baby developed impetigo on the ninth day and the mother suppurative mastitis on the twelfth day, the *Staphylococcus aureus* being cultured from the incised abscess.

*Recurrence and Mortality.*—The development of breast abscesses in subsequent pregnancies was not noted once in this series, so that we may conclude that one abscess does not predispose to the development of another in a future pregnancy. We may further conclude that one breast abscess does not preclude the mother from nursing her baby in a subsequent pregnancy unless that abscess has destroyed an appreciable portion of the glandular tissue, since 12 mothers in this series had 18 subsequent pregnancies, and in 17 instances nursing was accomplished with an average degree of success. Not a single death occurred in this series.

## CONCLUSIONS

1. The incidence of breast abscess in a series of 20,258 women delivered at or near term by the Obstetrical Service of the Johns Hopkins Hospital was 1 in 179. Among private patients even fewer cases were observed, 1 in 420 deliveries.

2. Race seems to play little if any part in the occurrence of breast abscess.

3. Suppurative mastitis is much more common in women nursing their first babies than in multiparas. Increasing parity seems to be a relative safeguard against its development.

4. The greatest number of cases develop during the third and fourth weeks of the puerperium, though 21 per cent of our series occurred after the thirty-ninth day postpartum and 6.2 per cent before delivery.

5. The average number of days between the onset of symptoms and the time of operation was found to be 10.82 days with a variation of six to sixty days. There were 71.3 per cent of the cases incised and drained within twelve days of the development of symptoms.

6. The inferolateral quadrants are the most commonly involved sites with more abscesses occurring in the right breast than in the left. Only 4.4 per cent were found to be bilateral.

7. A marked variation occurred from year to year and the condition seemed to develop more frequently in the colder than in the warmer months. This also coincided with the time of the year when upper respiratory infections were most prevalent, which suggests that foci of infection play a significant rôle.

8. In the great majority of instances the *Staphylococcus aureus* was the causative organism.

9. Notwithstanding the establishment of free drainage, it was found necessary to do secondary operations in 26.55 per cent of the cases.

10. One abscess does not predispose to the development of another in a future pregnancy, nor does it necessarily prevent the mother from nursing her baby in a subsequent pregnancy.

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## DYSTOCIA FOLLOWING THE INTRAUTERINE USE OF RADIUM\*

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**I**N A thorough search of the literature made in 1931, there were found only three reports of dystocia following the use of radium in the uterus.

Increased knowledge and skill in the use of radium have undoubtedly lessened its indiscriminate employment in cases of improperly diagnosed uterine bleeding during the childbearing period. That errors in judgment and technic are still being made, however, is shown by the fact that since 1929 three additional cases of dystocia have been encountered.

As the number of published cases is so small, the records of those previously reported will be included in this presentation.

**CASE 1.**—White, aged thirty-two, multipara, seen in consultation at the end of the sixth month of pregnancy, was being treated for aortic regurgitation. Eighteen months before the beginning of the present pregnancy, following a diagnosis of fibroids, radium had been inserted into the uterus. The result was menorrhagia, rather than amenorrhea, which continued for fourteen months. Four normal periods occurred during the treatment with ovarian extract; then menstruation abruptly ceased, and the patient was found to be pregnant. Pregnancy was uneventful until the end of the sixth month, when the membranes ruptured spontaneously and a loop of cord prolapsed through the cervix.

In the expectation that the onset of labor would follow the rupture of the membranes, nothing was done for twenty-four hours. As pains had not started at the end of that time it was thought best to deliver the patient. The cervix was long, indurated, barely admitted one finger and seemed to be absolutely undilatable. As the membranes had been ruptured and the cord had been in the vagina for twenty-four hours, the only method of abdominal delivery that seemed safe was a Porro cesarean. It was felt that the cardiac condition contraindicated this operation, and a vaginal cesarean was performed. The operation was exceedingly difficult as the induration was not confined to the cervix but extended well up into the uterine wall, necessitating long incisions, both anteriorly and posteriorly. The surgical recovery was uneventful, cardiac symptoms improved, but the patient remained in the hospital two months suffering from a severe puerperal psychosis.

**CASE 2.**—White, aged forty-one, primipara, seen in consultation. Three months after the last menstrual period, although the patient believed herself pregnant and was suffering from moderate hyperemesis, radium was applied for the treatment of cervical polyps. Seven months after the cessation of menses a roentgenogram showed no fetus. Three weeks later, however, two physicians positively heard fetal

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heart sounds and diagnosed an eight months' pregnancy. Two months later, intermittent pains began to occur in the lower abdomen. After seven days of severe labor pains, during which time the only rest obtained was an occasional short period of sleep from exhaustion, I was called in consultation.

Examination showed an irregular mass of boardlike rigidity reaching to 7 cm. above the umbilicus. Owing to the extreme hardness of the tumor and the irregularity of its outline, the diagnosis made was pregnancy complicated by fibroids and death of the fetus. The cervix was small, long, undilated, and showed no softening.

Laparotomy disclosed a uterus contracted so tightly around the fetus that it conformed to the irregularities of the body, giving the impression of fibroids when felt through the abdominal wall. The fetus was macerated, apparently at full term. The placenta and membranes were densely adherent to the uterine wall and were separated with difficulty. The patient made an uneventful recovery.

CASE 3.—White, aged forty, multipara, seen in consultation. Seven years before the beginning of the pregnancy, the patient had been curetted and treated with radium for the cure of metrorrhagia. Menstruation had continued and the pregnancy had been uneventful. Labor started at the expected date. After five hours of extremely severe pains, a contraction ring was noted at the level of the umbilicus. The cervix was long, hard, and closed. As rupture of the uterus seemed impending cesarean section was performed and sterilization was accomplished by resection of the tubes. A live baby, showing no deformities, weighing 6 pounds 9 ounces, was delivered. The placenta and membranes were densely adherent. Recovery was uneventful.

CASE 4.—White, multipara, seen in consultation after having been in labor for several hours. When the cervix had become fully dilated the attending physician ruptured the membranes. The cord prolapsed and a version was contemplated. On attempting to insert his hand into the uterine cavity, the physician found a dense cicatricial ring entirely surrounding the lower uterine segment, about 2 cm. above the external os. Radium had been employed in the treatment of uterine bleeding two years previously. A Porro cesarean was performed. The fetus was dead, but the mother's recovery was uneventful. This uterus has been saved, and an excerpt from the report of Dr. Choisser of the Department of Pathology follows:

"The ratio of the muscle and fibrous connective tissue is apparently normal in the body of the uterus, but in the cervix there is evidence of replacement of considerable of the muscle tissue by fibrous connective tissue. This is especially true in the left anterior quadrant of the cervix. The mucosa is hyperplastic with evidence of marked congestion and hemorrhage. It is irregular in contour with a few irregular tags of tissues adherent, apparently retained secundae.

"There is a tear extending from the left side of the external os, along the region of the attachment of the broad ligament and thence upward and anteriorly to within 4 cm. of the fundus of the uterus. In the cervix the tear is very irregular with extensive extravasation of blood into the mucosa, muscularis, and under the peritoneum, extending between the two layers of the left broad ligament. The extension of the tear into the body is straight with clean edges and a very small amount of hemorrhage into the mucosa. There is no evidence of neoplasia, either benign or malignant, or other specific pathology present in any part of this organ."

CASE 5.—White, aged twenty-nine, primipara. Several months after having been treated with radium for fibroids, the patient became pregnant. One month before the expected date she went into labor and after fourteen hours, the body of a baby weighing 3 pounds 8 ounces was delivered spontaneously. The head was arrested and moderate traction by the attending physician resulted in the separation of the



body from the head. Examination by me disclosed a dense, undilatable ring of connective tissue about 5 cm. in diameter, at the junction of the body of the uterus and the lower uterine segment. The decapitated head was in the upper portion of the uterine cavity. Puncture, crushing, and removal of the head was accomplished with extreme difficulty. Recovery was uneventful.

CASE 6.—This patient was seen in consultation by Dr. Jacob Kotz, through whose courtesy it is included in this report.

White, aged thirty-two, multipara. Had been treated with radium for uterine bleeding six months before the beginning of pregnancy. Three weeks after the estimated date of confinement a diagnosis of dead fetus was made and induction of labor, first medicinally and then by bag, was unsuccessfully attempted. A Porro cesarean section was performed and a macerated baby weighing 9 pounds was delivered. The entire cervix and the adjacent portions of the body of the uterus were found to be composed largely of fibrous tissue. Recovery was uneventful.

Comment is not necessary. Five infant-lives were lost and six women, although they recovered, were placed in extreme jeopardy.

The value of radium in the treatment of many pathologic conditions of the uterus is unquestioned. Unfounded criticism might deprive some patients of life-saving measures. These cases have shown, however, that in some instances at least, the musculature of the cervix and lower uterine segment has been replaced by fibrous tissue which constitutes an absolutely impassable barrier to the passage of the fetus. The inevitable conclusion is that radium therapy of the uterus may be employed with safety during the childbearing period only when sterilization has been unquestionably accomplished.

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Intensely acute pain which accompanies, for example, sudden torsion of an ovarian cyst or rupture of a pus tube is nearly always pathognomonic. This is due to the fact that the physical manifestations of this pain can easily be traced and because this type of pain cannot be simulated either consciously or unconsciously. Psychopathic individuals cannot feign such pain. Even though the exact cause for this type of pain cannot be detected, it demands both medical and often surgical attention.

Acute pain which accompanies, for example, salpingitis and Bartholinitis is often still more typical. Subacute and chronic pains are often difficult to trace but they are very common. In trying to find the cause the physician must determine if the pain is associated with an organic genital affliction such as metritis, fibroma, ovarian cyst, etc. If no definite lesion is found on examination, a psychic influence must be suspected. It must be remembered that the receptivity of a woman to pain is quite changeable and varies with different periods in the menstrual cycle.

## ABNORMAL DEVELOPMENT OF THE VAGINA AND GENITOURINARY TRACT

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IT IS quite true that theories regarding normal development should not be based upon studies of malformations and abnormalities, for serious misconceptions of embryologic processes may be, and have been brought about in this manner. But it is equally true that the study of abnormal development is of some value when made in the light of existing embryologic knowledge, and it is with this latter view in mind that we wish to give a description of a female fetus showing a number of abnormal features, and to discuss the conditions we have found in the genital tract. We are of the opinion that these conditions are of some interest when surveyed in their relation to the existing theories of vaginal development.

It may be said here that quite a number of divergent views are held regarding the vagina; divergent not only as to the embryonic structure or structures from which that organ is developed, but also as to the method of formation. No useful purpose would be served by a detailed survey of the literature of the subject but it is here necessary briefly to outline the problems which still await solution.

It not yet quite clear if the vagina in the human female be developmentally compound or not, that is, if more than one embryonic structure be concerned in the formation of the adult organ. Since there are these different views about the matter, there are correspondingly variable opinions concerning the embryonic structures from which the vagina may be formed. Even those who hold that the vagina is developmentally simple are not in accord regarding its source of origin, and we thus find that some of these observers hold it to arise from the müllerian ducts, others believe it to be formed from the wolffian ducts, and yet others make it a derivative of the urogenital sinus. Similarly those subscribing to the view of the compound origin of the vagina believe the upper portion to be formed by the müllerian ducts while the lower portion arises from the wolffian ducts or the urogenital sinus, or from both. In our study of this fetus then we have borne these conflicting views in mind.

### DESCRIPTION OF SPECIMEN

In brief, this specimen is a female fetus showing multiple developmental abnormalities including spina bifida with a large meningocele, umbilicus membranaceus with herniation of most of the abdominal contents and epispadias, ectopia vesicae, and split pelvis. The large bowel was represented only by a closed sac at the cecum, and there was no anus. The interest in the case, however, centers about the internal genitalia.

The fetus was delivered by a colored multipara, aged thirty-four years, 261 days after the onset of the last menstrual period. The fetal heart was heard on admission but the child was stillborn. It had a sitting height of 25 cm. and a total length of 36.5 cm.

The membrane covering the ventral hernia was ruptured at the time of delivery and the viscera protruded through the opening.

Autopsy showed no abnormality of the structures above the diaphragm. The vertebral canal was open posteriorly and this involved all of the lumbar and sacral vertebrae. A meningocele containing a large amount of fluid was found as shown.

Examination of the abdominal contents showed normal structures except that the small bowel ended in a blind pouch of cecum which was adherent to the posterior surface of the internal genitalia. No further evidence of large bowel could be found.

A thin margin of normal skin separated the membranous ventral wall from the bladder. The latter was open on the ventral surface and in its wall could be seen the ureteral orifices. On the upper portion of the bladder wall (see Fig. 2) was a mound of tissue covered by a wrinkled, delicate skin. A slitlike opening on its



Fig. 1.—Lateral view of child as at delivery.

upper surface gave one the impression that it resembled a clitoris with its prepuce, the whole turned upside down. Lateral to this were wing-shaped sheets of mucosa with small craters on the surface. This ended abruptly as though adherent upon the bladder. The lateral wings were continuous with one another cephalward to the mound.

A dimple in the skin only large enough to admit a small probe was found where one would expect to find the anus. The skin of the perineum was otherwise smooth and showed no evidence of the formation of the external genitalia. The small opening led into the epithelial tube shown in longitudinal section in Fig. 3. This opened on the ventral surface on the upper side of the mound as described above.

Microscopic examination of this tube showed that it was lined by a thick stratified epithelium covered on its surface by shed squamous cells. The base was fairly regular but was indented by papillae and perforated by gland ducts. The stratum germinativum contained pigment. In the subcutaneous tissue were many sebaceous glands, a few sweat glands, and some hair follicles.

Just beneath this tube, a little lateral to the midline and at the base of the mound described was a mass of erectile tissue presenting the usual characteristics. Numerous nerves were scattered through the musculature of the mound.

The mound was covered by an epithelium similar to that of the tube. In the former, however, it was somewhat thicker and more indented by papillae. The subcutaneous tissue here presented neither gland structures nor hair follicles. This epithelium blended into a thicker epithelium at the base of the mound. This

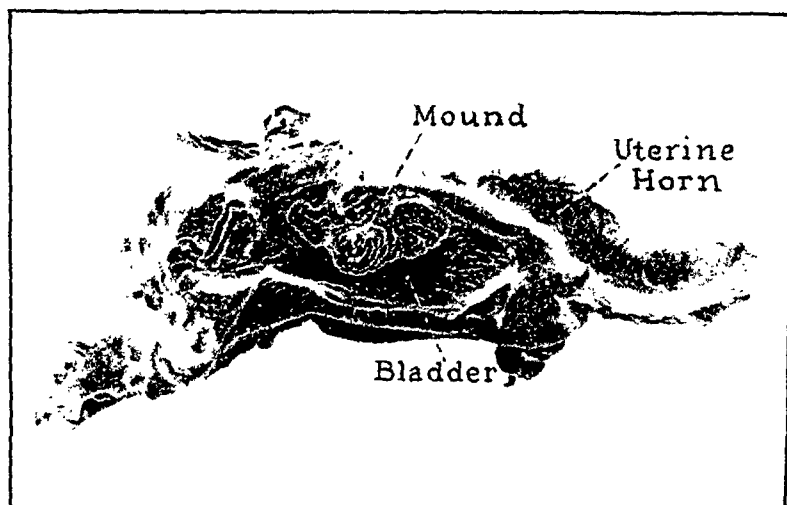


Fig. 2.—Pelvic organs and exposed bladder wall. The left uterine horn and the left ureteral orifice may be seen.

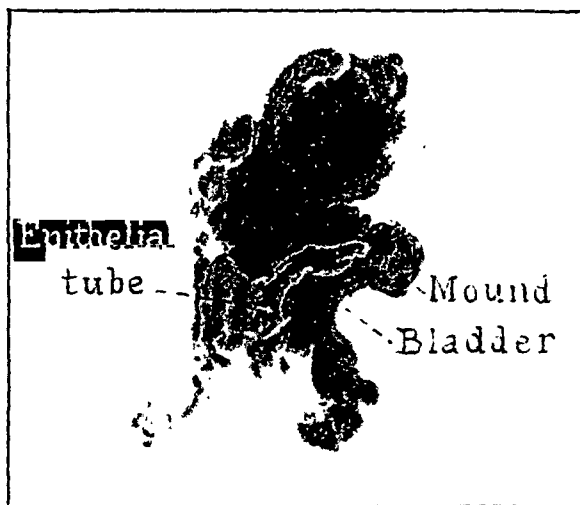


Fig. 3.—Transverse section of pelvic organs shown in Fig. 2 taken just to the right of the midline.

latter, which formed the wing-shaped structures seen in Fig. 2 was thick, its cells large with pale cytoplasm and well-marked cell boundaries. It was not similar to bladder mucosa but was squamous in type and showed many nerves in the musculature below it. Elsewhere the mucosa of the bladder had been lost and the wall was naked and in places necrotic.

The pubic bones were separated to produce a split pelvis. About 1 cm. lateral and caudal to the anterior superior spines of the ilium were small raised nodules of pigmented skin which might represent labia majora.

The internal genitalia were of particular interest. Directly behind the bladder and a little to the right of the midline was a blind sac measuring 2 cm. in diameter. Extending laterally from this were two uterine horns, that on the left measured 7 cm. in length and from 1.2 to 1.5 cm. in diameter, the right horn being 4 cm. long and 1 cm. in diameter. Both ended abruptly in small fallopian tubes whose ends were adherent about what proved to be normal ovaries. The central sac contained a greenish yellow opaque mucoid material. Opening laterally into the sac were the cervixes, each of which contained a small amount of clear mucus. The two cervical canals were the only openings from the sac.

Microscopic examination showed the uterine horns, the tubes, and the ovaries to be normal. The central sac showed a normal vaginal mucosa thrown into folds. It was thick, had a smooth margin toward the submucous tissue and varied from 8 to 12 cells in thickness. The submucosa with its vascular supply and musculature was that of the normal vagina. This could be seen to blend into the cervical structures in the usual manner.

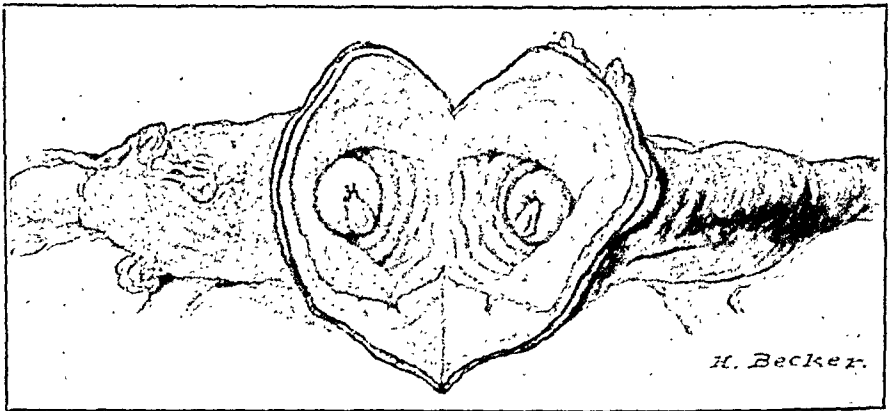


Fig. 4.—Drawing of the internal genitalia. The uterine horns may be seen with their cervixes opening into the incised vaginal sac.

#### DISCUSSION

Ectopia vesicae would seem to occur less frequently in females than in males. Gruber (1927) states that the ratio of females to males is about 1 to 8, and the malformation is commonly associated with extensive pelvic defect and often with meningocele. The mode of formation of the bladder defect in this case is to be ascribed to a breakdown of the ventral wall of the urogenital sinus in its entire length. The condition is not a persistence of the cloaca since we could discover no communication between the caudal end of the gut and the exposed dorsal wall of the urogenital sinus.

The epithelial tube containing the structures of external skin which ran from the anal region to open on the mound on the bladder wall cannot be explained. It is suggested that this belongs to that group of anomalies developing in the absence of normal surrounding structures, and which in their final form cannot be related to any normal process of development.

The condition of two uteri and two cervixes is a well-recognized malformation of the female genital tract and is to be explained by an almost complete nonunion of the urogenital folds which contain the müllerian ducts in early embryonic life. It is not proposed further to consider this portion of the genital tract in our specimen, since we are not in a position to make any suggestion of value regarding the etiology of the condition other than to indicate the association here with extensive defect of the pelvic organs.

We believe that the blind sac into which the two cervixes open must be regarded as the vagina. The histologic appearances of the epithelium lining the sac and the arrangement of the muscular fibers in its wall are similar to those at the cervico-vaginal junction in the normal full-term fetus. Further, the anatomic relations of this sac leave no doubt in our minds that it represents only the upper portion of the vagina and that the lower portion of that organ as well as the hymen are not represented in the specimen. Such a condition is mentioned by Kermauner (1912) as occurring in some cases of uterus bicornis associated with ectopia vesicac. It is rather difficult to reconcile this condition with those views which make the vagina a developmentally simple organ, and especially with those views which derive it entirely from a structure other than the müllerian ducts. Thus Vilas (1932) holds the entire vagina to be developed as a solid epithelial plate which grows in a cranial direction from the wall of the urogenital sinus displacing the fused lower ends of the müllerian ducts upward until the latter are at the level of the future cervix. The epithelial plate is subsequently canalized to produce the tubular vagina. A somewhat similar description of the process is given by Kempermann (1931) with the exception that he derives the epithelial upgrowth from the lower ends of the wolffian ducts. These descriptions fail to explain the development of a normal upper portion for the vagina with complete absence of the lower part.

It would seem that this specimen is more reasonably explained by those theories which make the vagina developmentally compound. Mijsberg (1924) has put forward the view that the upper portion of the vagina (about two-thirds) is developed from the fused müllerian ducts while the lower portion is a product of the wolffian ducts. Koff (1933) holds a similar view concerning the derivation of the upper portion of the vagina but thinks that the lower portion arises from the epithelium of the urogenital sinus. The abnormality under discussion would seem to be readily explicable by either of these theories if the growth of the lower developmental component were for any reason to be inhibited. It is quite clear that there has been arrest of development of the urogenital sinus at an early stage in this fetus with breakdown of the ventral wall; but the evidence before us does not enable us to make any statement concerning the normal derivation of that segment of the vagina which is lacking in our specimen. Since the urogenital sinus and the lower ends of the wolffian ducts are normally so intimately associated it is conceivable that arrest in development of the one structure might react upon the other, so that the conditions we have found might be used to support the claims of either the urogenital sinus or the wolffian ducts for the formation of the lower end of the vagina with equal justification. It is our opinion, however, that this specimen strongly supports the view that the vagina in the human female is formed from more than one embryonic structure.

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# ERGOT AND ERGOTAMINE TARTRATE IN PUERPERAL PROPHYLAXIS

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**P**ROPHYLACTIC measures that tend to lessen maternal morbidity should be welcomed. We offer the results of this study for whatever purpose they may serve in the improvement of the situation.

This report is based on 169 consecutive obstetric patients at the Coney Island Hospital, representing 171 deliveries. Our prophylactic, postpartum measures, aside from the regular routine, consisted in the administration of fluid extract of ergot, or its alkaloid, ergotamine tartrate, and a control group. This study was spread over a period of forty-five days. During the first fifteen days all patients delivered received ergotamine tartrate; the second fifteen days, ergot; and those delivered during the third period of fifteen days were used as controls. Each patient received 30 minims of ergotamine tartrate daily for three days, divided in 5 doses of 6 minims each, so that all medication was administered during the patient's waking hours. Fluid extract of ergot was given in 15 minim doses, 4 times per day, over a period of three days. As a result of this arrangement, 67 patients received ergotamine tartrate, 49 received fluid extract of ergot, and 53 were used as controls.

Sühs, in a similar study, using ergotamine tartrate in 53 selected cases, found that 57 per cent of these had what he called an "undisturbed puerperium." Of 53 control patients only 6 per cent had an "undisturbed puerperium." By a "disturbed puerperium," Sühs refers to an abnormal change in the lochia or a delay in the involution of the uterus.

The following factors were considered in this study: Length of time in labor, number of vaginal examinations, method of delivery, weight of child, and complicating, nonobstetrical conditions.

The length of time in labor varied from twenty-five minutes to fifty-nine and two-thirds hours. The distribution in the various groups is best shown in Table I.

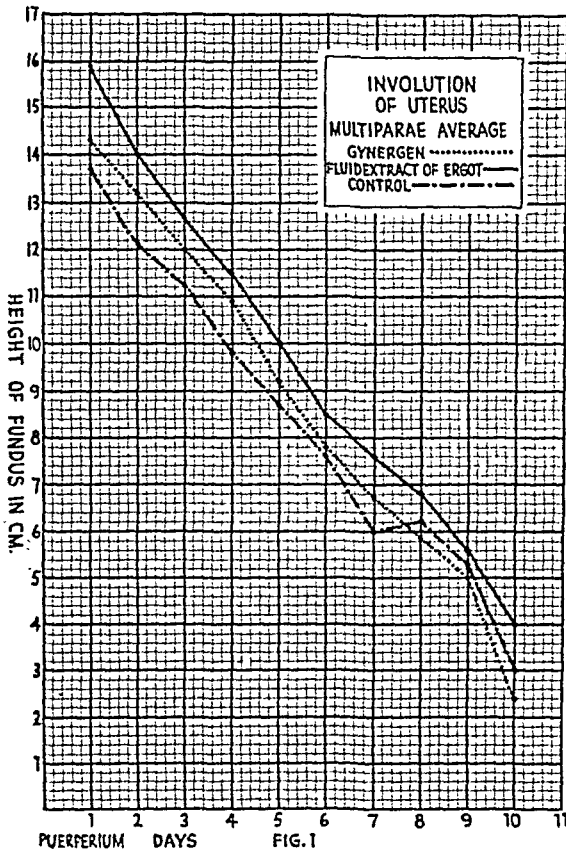
TABLE I. DURATION OF LABOR IN HOURS AND MINUTES

	MULTIPARAS		PRIMIPARAS		TEMP. GROUP			
					MULTIPARAS		PRIMIPARAS	
	SHORT	LONG	SHORT	LONG	SHORT	LONG	SHORT	LONG
Control	1.15	47.20	3.55	44.40	3.15	4.35	7.10	35.05
Ergot	2.0	59.40	6.0	24.0	3.15	29.05	30.55	45.0
Gynergen	0.25	58.55	4.0	57.35	1.20	27.35	6.15	57.15

Routine vaginal examinations are not sanctioned on our service. However, when indicated, under proper aseptic precautions, they may be done. Rectal examinations are employed to follow the progress of labor.

There were 149 spontaneous deliveries, 9 forceps and 13 breech. There were two sets of twins. There were two stillbirths, one due to an unrecognized, prolapsed cord, the other followed a forceps delivery. Manual removal of the placenta was resorted to in one case.

The smallest baby weighed 1,800 gm., and the largest 4,840 gm.; 44 per cent of all our babies weighed over 3,600 gm.



Among the complicating conditions, there was one case of old tuberculosis, with a bronchopneumonia, one case of acute tonsilitis which set in on the tenth day, one of typhoid fever, and one patient with lobar pneumonia was admitted in labor. There were two acute mastitis cases and two of acute pharyngitis.

Although the weight of the baby, the length of time in active labor, the amount of manipulation, the mode of delivery all play an important rôle in the morbidity of the lying-in period, still the gauge for such morbidity is the temperature.

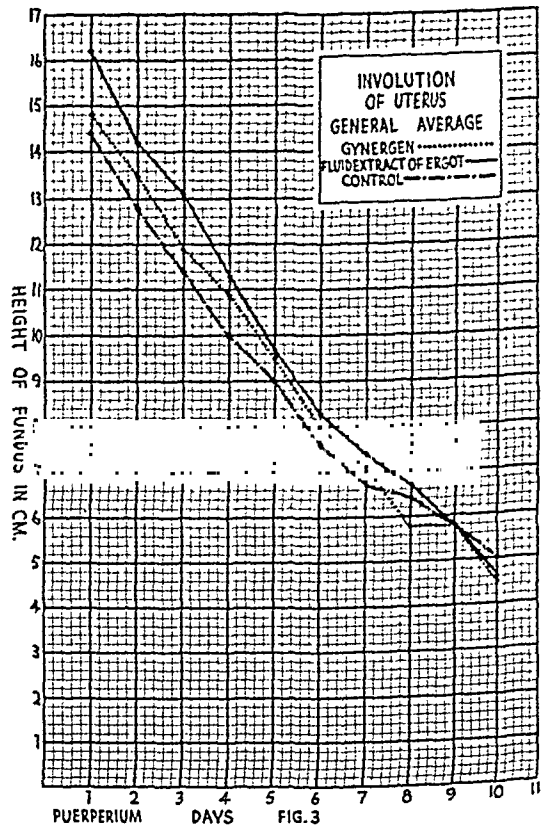
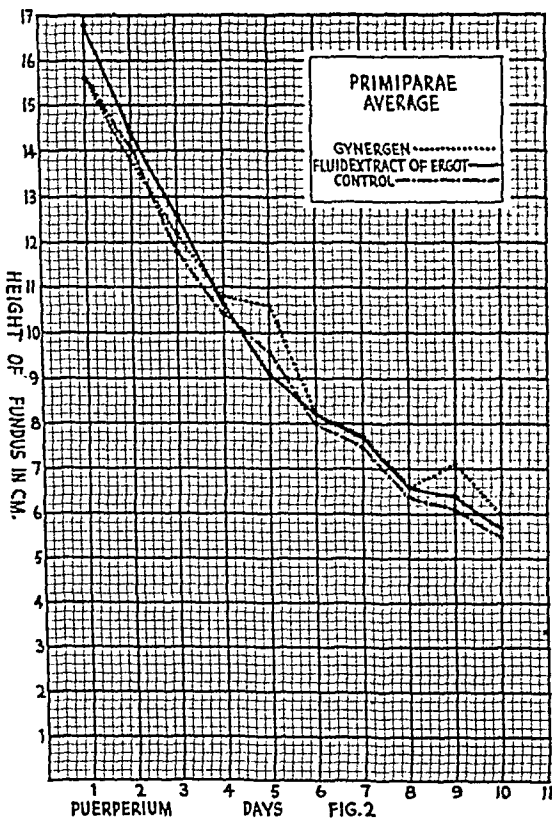
The choice in this study, of an arbitrary line of demarcation between a normal temperature and a morbid temperature presented a problem. It seemed unjust to call only such patients with a tempera-



ture of  $100.4^{\circ}$  F. on two successive days other than the first, as being morbid, when 16, or almost one-third of all the fluid extract of ergot series had a temperature range of  $99^{\circ}$  F. to  $99.8^{\circ}$  F. from two to five days during the lying-in period. A like situation existed in the control series. In striking contrast, only 13.4 per cent of all those receiving ergotamine tartrate had a temperature on any two or more days of  $99^{\circ}$  F. or  $99.8^{\circ}$  F.

Hampton and Wharton in 1920, reviewing a series of embolic deaths, found one positive factor, which was a persistent temperature of from  $99^{\circ}$  F. to  $100^{\circ}$  F. They concluded that such temperature indicated a low grade infection somewhere. They quoted similar statements by Michaelis, G. Petren, and Mahler.

If we followed the accepted standard, our total morbidity in this series would have been 3.5 per cent. We believe that this is a fair



result, when we consider the overcrowding in our wards and the size and weight of our babies.

*Lochia.*—All cases in the control series had some lochia at the time of their discharge on the eighth to the tenth day of the puerperium. Lochia rubra was present in over 79 per cent of the cases. In no case was there an absence of the lochia. In 4 cases it was termed scant. Forty per cent of the fluid extract of ergot cases showed an absence or change in the character of the lochia at the time of discharge as compared with 30 per cent of the ergotamine series. How-

ever the latter group showed a scanty lochia in 61 per cent of the patients in contrast to 46 per cent of the fluid extract of ergot cases.

The importance of this is readily seen in a review of the temperature charts. The ergotamine tartrate group had a corrected morbidity, according to the stricter classification, of 14.9 per cent as compared with a 40 per cent and 53 per cent, respectively, in the fluid extract of ergot and control series.

With regard to involution under such stimulation, the general average for all seems to show a better involutionary response to ergotamine tartrate. This is more evident in the multipara (Figs. 1 and 2). Involution in the primipara, however, seems to progress better when left alone. (Fig. 3.)

#### SUMMARY

In a series of 169 consecutive parturients delivered under the same conditions we find that many patients had a mild temperature, not high enough to be put in the accepted morbidity group, yet of sufficient persistence to make one realize that all was not quite well. In the group with the greatest number of temperature cases (53.15 per cent, the control group), lochia rubra persisted beyond normal expectancy; there was some form of lochia present at the time of discharge, and involution had not progressed as well in the multiparas as in the primiparas. The administration of ergot and more particularly its alkaloid, ergotamine tartrate, prophylactically, hastened involution, lessened lochia rubra, and checked lochial discharge by the tenth day.

#### CONCLUSIONS

From this study it would seem justifiable to draw the following conclusions:

1. The administration of ergot or its alkaloid, ergotamine tartrate, during the first three days of the puerperium hastens involution and lessens the lochial discharge during the parturient's stay in the hospital. Ergotamine tartrate, as shown by this study, accomplishes this better than the usual preparations of ergot.

2. Our series, of course, is too small to warrant definite conclusions. We believe, however, that enough positive data have been presented to warrant further investigation of the use of oxytocics during the puerperium.

I wish to thank Dr. Harvey B. Matthews, Director of the Obstetric Department, for his interest and suggestions in the preparation of this paper.

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## DYSTOCIA DUE TO DILATATION OF THE FETAL URINARY BLADDER

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School of Medicine)*

E. G., twenty-two years old, colored, para vii. Typhoid fever, uncomplicated, at six years of age. No history of syphilis, tuberculosis, or other diseases. First pregnancy terminated in a full-term stillborn child, cause unknown. During the 5 succeeding pregnancies she was delivered by our clinic as an unregistered case. Each time her Kolmer reaction was negative and the pregnancies terminated spontaneously at twenty weeks, twenty-four weeks, twenty weeks, twenty-three weeks, and twenty-two weeks, respectively. The causes for these abortions are unknown. All of the fetuses were male, and all the puerperiums were normal. Physical examinations were negative except during her fifth puerperium when there was a slight diffuse thyroid enlargement.

Last menstrual period Sept. 14, 1933. Pregnancy uneventful. The Kolmer reaction was again negative. Without warning or pain the patient bled a small amount with dark clots on the eighteenth of February, 1934, and in an hour labor pains started. Labor appeared to be progressing normally and at 12:45 A.M., Feb. 19, 1934, the head was delivered. There was no further progress and the pains became weak and irregular. Bleeding had ceased with the descent of the head and did not recur after its delivery. All efforts to deliver the remainder of the fetus by traction were unsuccessful. The patient was then examined vaginally and a large, cystic, tense fetal abdomen was discovered. One finger was easily forced into the fetal umbilicus, releasing a considerable amount of clear fluid under pressure. The remainder of the delivery was then easily accomplished without further delay at 1:30 A.M. on the same date, the patient being delivered of a twenty-eight-week dead male fetus measuring 35 cm. in length and weighing (1,132 gm.) 2 pounds 8 ounces.

Placenta, membranes, and cord appeared normal. Because of the unusual history of this case a Kahn test was performed on the blood of the patient's husband, the result being strongly positive.

### THE FETUS

*Gross.*—The fetus (Fig. 1), male, measured 35 cm. in length. The head was cyanotic and separated from the vertebral column, though not from the body. The costal margins and xiphoid process were on the same plane, and the thorax was markedly compressed. The abdominal wall was cyanotic and quite redundant and wrinkled, having been punctured at the umbilicus and the insertion of the umbilical cord destroyed. The genitalia appeared normal but the testes had not descended into the scrotum. The only other gross anomaly noted was bilateral talipes equinovarus. The anus was perforate. A purse-string suture was placed about the aperture in the abdominal wall. The large bladder was filled with formalin, 1,000 c.c. being necessary to fill the cavity without forcing the fluid under pressure. The entire fetus was fixed thus and frozen when a median sagittal section was made (Fig. 2).

No evidence was seen of intracranial injury, and no gross abnormalities were noted in the heart, lungs, or trachea.

The abdomen had been perforated at the umbilicus and no evidence of a membranous area in this region as described by Spicer and Schwyzer in their cases could be found. The most striking feature was the urinary bladder which had been so distended that it compressed all the abdominal viscera and caused deformity of the thorax (Fig. 2). The bladder was loosely attached to the abdominal wall.

The peritoneum showed no signs of inflammation, and there was no ascites.

The stomach, intestines, liver, gallbladder, pancreas, and spleen appeared normal grossly. There was no communication between the intestinal tract and the bladder.

The bladder was greatly dilated, in the midline, and consisted of a single cavity spherical in shape with uniform outline. The wall varied in thickness from 1.48



Fig. 1.

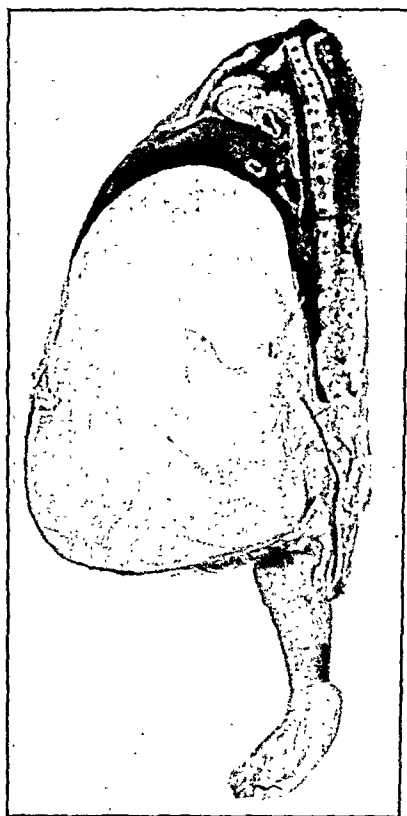


Fig. 2.

mm. to 0.4 cm. at the urethral orifice. The interior of the bladder was smooth and fairly even and measured 16 by 12 by 10 cm. The ureteral orifices were 8 cm. apart, and the right 4.5 cm., and the left 5 cm. from the urethral orifice.

Beginning at the vesical orifice a probe passed easily through the urethra until a point 0.3 cm. from the external urinary meatus was approached where it stopped. Proximal to this obstruction the urethra was markedly dilated measuring 0.4 cm. in diameter. (Black thread in Fig. 2 is in the urethra). At the point of obstruction there was a marked narrowing of the lumen of the urethra to 0.19 mm. measured in serial sections of the spongy urethra. No complete obstruction could be demonstrated, and no other abnormality of the urethra was noticed.

The ureters were dilated, the right and left measuring 1.0 cm. and 1.7 cm. in diameter, respectively, at their widest points. They were tortuous but no obstruction was demonstrable in either. Fig. 3 shows the left kidney, adrenal, ureter, testicle, and the left half of the bladder.

The kidneys were lobulated and showed no cysts. The pyramids were somewhat flattened and the pelves dilated, but the kidney substance did not appear to be affected. The right kidney measured 3.5 by 2 by 1 cm., and its pelvis 1.5 by 0.75 cm.; while the measurements of the left kidney and its pelvis were 3 by 2 by 1 cm. and 1.6 by 0.9 cm., respectively. The adrenal glands appeared normal.

The left and right kidneys, adrenals, and testes exhibited normal histology. The bladder wall was 1.48 mm. in thickness and appeared normal histologically although there was evidence of hypertrophy in the muscular wall. Fat stain was negative for intracellular as well as intercellular fat. Sections of the liver showed normal architecture; and in those stained by Levaditi's method no *Spirocheta pallida* were found. Rugae in the left ureter had been smoothed out and evidences of edema and muscular hypertrophy were present. The ureteral wall was 0.26 mm. in thickness from its mucous membrane including the tunica adventitia. The right ureter exhibited the same picture to a lesser degree. The rugae were slightly flattened and the lumen was large. The wall measured 0.18 mm. in thickness. Serial sections of the distal half of the penis demonstrated a marked stenosis of the

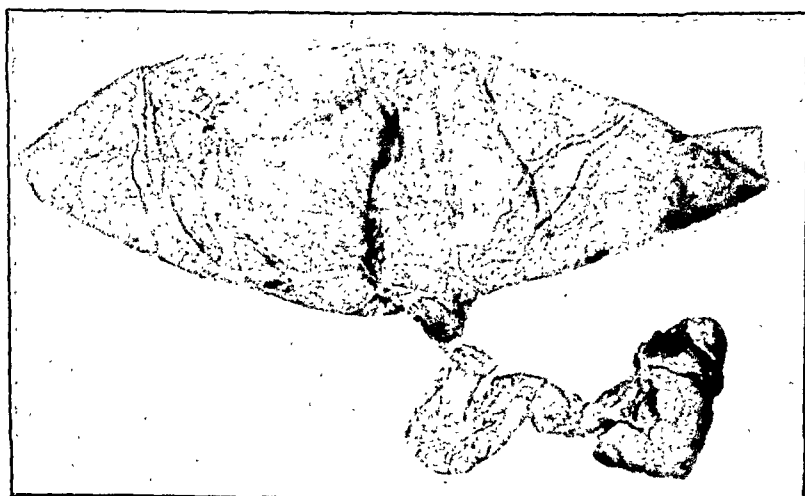


Fig. 3.

spongy urethra at its distal extremity. At its narrowest point the lumen measured 0.19 mm. in diameter. No actual obstruction was found.

The fluid was pale yellow in color and water-clear in transparency. Its reaction was alkaline to litmus and acid to phenolphthalein; and its hydrogen ion concentration by the colorimetric method was 7.4. The specific gravity was 1.0075. By Marshall's urease method urea was found to be present to the extent of 0.36 per cent; while chlorides as sodium chloride were found to be 0.17 per cent by the Volhard-Arnold method. Albumin was present to the extent of less than 0.003 per cent. There was no odor. Acetone, diacetic acid, blood, and bile were absent.

Microscopic examination of the centrifuged specimen showed two types of cells:

1. Epithelial cells of the squamous type were found in small numbers only, but were typical in size, shape, and grouping. Dispersed throughout their protoplasm, but not in the nucleus, refractile droplets were seen which varied in size the largest of which were about one micron in diameter. By suitable staining methods these droplets were seen to be lipid in character.

2. A large number of cells of a second type were seen. They were larger than the polymorphonuclear leucocyte and showed predominantly a large, single, round or horseshoe nucleus. In these cells also the lipid droplets were present but the

individual droplets were larger. These cells stained with the blue dye only when stained with eosinate of methylene blue.

In view of the absence of both sugar and larger quantities of protein it was felt that the possibility of the fluid's being a transudate was ruled out.

Walther reports the finding of epithelial cells and fat droplets in the fluid in his case but records no intracellular lipoid droplets.

I wish to express my sincere appreciation to Drs. J. M. H. Rowland and L. H. Douglass of the Department of Obstetrics; Drs. H. R. Spencer and C. G. Warner of the Department of Pathology; and Dr. H. B. Wylie of the Department of Biological Chemistry for their aid and suggestions during the preparation of this paper.

UNIVERSITY HOSPITAL.

## RUPTURED PREGNANCY IN THE CLOSED RUDIMENTARY HORN OF A BICORNATE UTERUS

### EXTERNAL MIGRATION OF THE SPERMATAZOOON; URINARY SUPPRESSION FOLLOWING TRANSFUSION

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THIS case of pregnancy in the closed accessory or rudimentary horn of a bicornate uterus is reported because of its rarity, and the nature of the transfusion death, and to record a definite instance of external or peritoneal migration of the spermatazoon.

M. S., German, aged twenty-eight, married eleven months, was admitted to St. Catherine's Hospital on March 18, 1933, complaining of abdominal pain. Her last menstrual period occurred on Oct. 12, 1932, with a previously regular 28/4 menstrual cycle without pain or discomfort at any time.

She had sought no prenatal care in this, her first, pregnancy, and had been apparently well until the evening of March 15 when she suffered severe crampy pain in the abdomen, pain in both shoulders, and vomited. She felt better the next day but stayed in bed. The next day, however, forty-eight hours after the first pain, she felt terrific pain in the abdomen and fainted, falling so heavily against the bathroom door, that she sustained a very severe contusion of the cheek and chin, where a wide area of ecchymosis and a hematoma were present.

She was a well-developed young woman, very pale, with lips, conjunctivae and mucous membranes almost white, dry tongue, pulse 120, small and of poor quality. Her skin was cold. Heart sounds were of poor muscular quality. Blood pressure was 120/65; temperature, 99.3; respiration, 24; R.B.C., 1,950,000; W.B.C., 14,700; polymorphonuclears, 87; Hg, 36 per cent. Urine was negative.

The abdomen was generally rigid, with marked peritoneal rebound pain, shifting dullness in the flanks, and a firm, somewhat tender mass thought to be uterus, but all to the left of the median line, extending 4 cm. above the umbilicus. Fetal heart could not be heard. The cervix was soft, continuous with the mass felt abdominally, and there was no history or evidence of vaginal bleeding.

A diagnosis of ruptured cornual pregnancy was made, and laparotomy under procaine infiltration and gas oxygen anesthesia presented no difficulties. The time of operation was twenty-one minutes. Through a midline incision below the umbilicus, a large amount of blood, over 3,000 c.c., poured out of the peritoneal cavity. A large male fetus lying free was attached by its umbilical cord to a placenta which, with its membranes, was but slightly adherent to the cavity of a well-contracted uterus

which was turned inside out through a rent  $3\frac{1}{2}$  inches long, low on its posterior surface. Another uterus about the same size, 3 months' gestation, with normal tube and ovary attached, was seen to the right. After extraction of the fetus, placenta, and membranes, the ruptured uterus was removed supracervically with the left tube and ovary, which showed the corpus luteum of pregnancy, cutting through a bridge about one and one-half inches long and one inch wide which tied it to the other uterus; the abdomen was closed in layers.

Operation was preceded by transfusion of 320 c.c. of whole blood, Scannell method, and followed by 520 c.c. of whole blood given the same way. Cross agglutination of donor and recipient showed compatible blood, but grouping was not done. No immediate reaction of any kind was noted during either transfusion.

She stood the operation well, and returned to the ward in fairly good condition, but restless. Veniclysis was begun through a cannula which had been left in the vein. She appeared to be better the next day though skin and sclerae showed orange-red jaundice, and only a few drops of urine had been obtained by catheter eighteen hours after operation. During the next seven days, she was catheterized once daily,

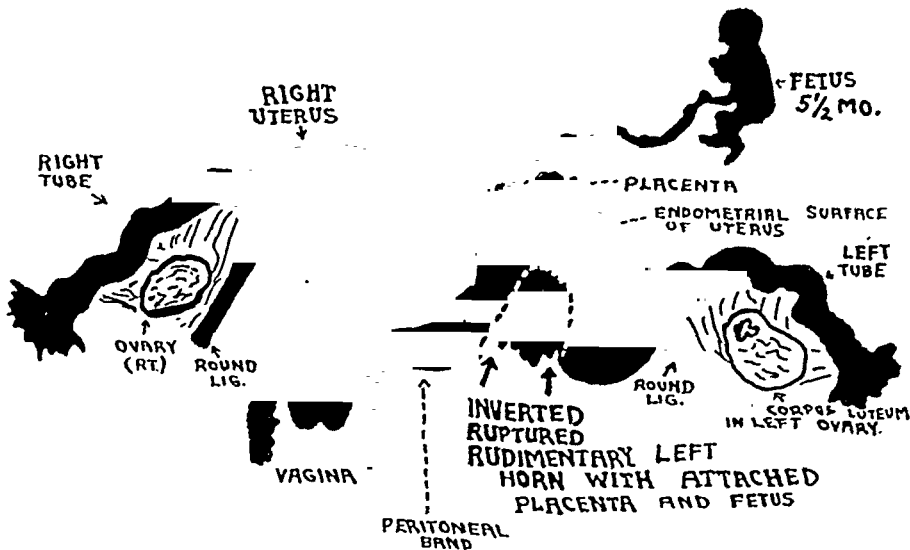


Fig. 1.—Bicornate uterus with rudimentary horn (ruptured).

obtaining nothing or as much as 8 ounces, a total of 29 ounces for this whole period. Blood pressure rose to 150/78. She vomited repeatedly large amounts of brown or black fluid which contained blood. Slight vaginal bleeding began on the day after operation and continued for five days. There was no edema. She remained conscious, though drowsy and apathetic, until she died on the twenty-ninth, eleven days after operation. On the last two days she had voided 30 ounces of urine each day, and her blood pressure was 168/90. Treatment consisted of gastric lavage, glucose veniclysis and drip, saline clysis, colonics and two hot packs.

Except for blood on two occasions, the urine showed only a heavy trace of albumin and an occasional hyaline cast in several postoperative examinations. The blood on the twenty-fifth showed: Urea nitrogen 161 mg. per 100 c.c., sugar 150 mg., creatinine 4 mg.; on the twenty-seventh, urea nitrogen 161 mg., sugar 140 mg., creatinine 4 mg.; on the twenty-ninth, urea nitrogen 224 mg., sugar 180 mg., creatinine 12.5 mg. Blood counts showed: On the twenty-third, R.B.C. 2,400,000, W.B.C. 18,400, polymorphonuclears 81 per cent, Hg, 41 per cent; on the twenty-ninth, R.B.C. 2,620,000, W.B.C. 31,000, polymorphonuclears 84 per cent, Hg 51 per cent; moderate achromia, poikilocytosis, anisocytosis, and polychromatophilia were always present.

## NECROPSY AND PATHOLOGIC REPORT

Necropsy consent was limited to opening the incision which was found well healed. The spleen and liver were not seen, but appeared normal on palpation. The stomach was dilated and filled with fluid. The large and small intestine were normal. There was no free fluid, and no evidence of peritonitis.

The remaining uterus was twice normal size, its cavity communicating with a normal cervix and a normal tube and ovary. The well-healed muscular stump of the excised uterus was attached to this uterus just above the cervix by a connecting bridge terminating in two folds of peritoneum separated by a small amount of areolar tissue. Obviously there could be no communication with the other uterus or its cervix, and none could be demonstrated. The rudimentary horn showed a wall 3 cm. thick except below the line of rupture where it was very thin. Typical corpus luteum of pregnancy, one-fourth the size of the ovary, was present in the left ovary.

The kidneys were pale and large, with easily stripped capsules and soft gray cortex; the markings of the medulla were accentuated. The right kidney was  $1\frac{1}{2}$  times normal size with a normal ureter which was followed to the bladder. The left kidney was 3 times normal size and appeared to be two kidneys fused with a double pelvis and two ureters with two bladder orifices, patent throughout. Microscopically the kidneys were adematous with accumulations of small round cells between the tubules. The glomeruli were swollen, with dilated capsules. The collecting tubules showed granular degeneration and masses of brown pigment (hemoglobin) more abundant and more deeply staining in their distal portions.

## COMMENT

The corpus luteum of pregnancy was found in the left ovary. The closed rudimentary horn of the bicornate uterus was on the left side, and clearly not in communication with the cervix. Fertilization was possible only by external migration of the spermatozoon. Hartman believes that movements of the viscera may move the spermatozoon about until chance brings it in contact with the infundibulum.

The clinical significance of developmental duplication of the uterus is obvious. In the early months, diagnosis of pregnancy in a rudimentary horn is possible, for the diagnosis was made in 20 per cent of Kehler's 84 cases collected in 1900. Whether diagnosis is made by rectal palpation of the connecting band, or by feeling the round ligament distal to the mass instead of proximal as in tubal pregnancy, for practical purposes diagnosis must depend upon observation of a tumor corresponding to the duration of pregnancy next to an only slightly enlarged uterus.

Urinary suppression as a delayed reaction to transfusion is probably not rare. In 1931, James Bordley reported three cases, and gathered fourteen more from the literature of transfusion since the recognition of blood groups. In an excellent and thorough analysis of these cases he showed that in not a single case was there conclusive evidence that the bloods of donor and recipient were compatible, although he was aware that Ottenberg and Johnson described an incompatible type of reaction occurring even when donor and recipient were of the same blood group. The method of transfusion was unimportant. The amount of blood injected was significant; no patient receiving less than 340 c.c. died, and none receiving more than 540 c.c. recovered. Oliguria, vomiting and uremia were outstanding symptoms of the delayed reaction. The renal lesion was an unusual one yet always the same, and very similar to the lesion found in this case.

Bordley offers four possible explanations of the mechanism of the kidney damage: (1) Mechanical blockage of tubules, (2) anaphylactic shock, (3) metabolic disturb-



ance due to loss of chlorides following persistent vomiting, (4) toxic substances in the incompatible blood.

Johnson and Conway, in August, 1933, reported three similar cases. In one of their cases, however, cross agglutination and blood grouping were done, and repeated after transfusion; no incompatibility could be demonstrated.

### SUMMARY

1. A case of pregnancy in the closed rudimentary accessory horn of a bicornate uterus is reported. Rupture with massive intraperitoneal hemorrhage occurred in the fifth month and was preceded by partial rupture forty-eight hours before.

2. Fertilization was effected by external migration of the spermatozoon.

3. Death was due to a delayed transfusion reaction characterized by oliguria, vomiting and the uremic syndrome, and probably caused by the injection of incompatible blood, although cross agglutination had seemed to show no incompatibility.

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256 JEFFERSON AVENUE.

## VAGINITIS EMPHYSEMATOSA

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IN 1877 Zweifel gave the name of "vaginitis emphysematosa" or "colpitis emphysematosa" to inflammation of the vagina occurring most often during pregnancy and characterized by collections of gas in the mucosa which caused bleblike elevations. On analysis he believed the gas to be trimethylamin. Many observers termed this disease "colpolhyperplasia cystica," which is probably a misnomer, as the gas present has no well-defined walls or boundaries except as it may occasionally be contained in the lymph vessels. Jackson and Wright, Heaney and others have reported cases of this disease which followed hysterectomy. Hugier in 1847 probably was the first to describe this condition. There are very few complete descriptions in the English or American literature, possibly because this type of vaginitis has very little clinical significance. In the German literature are many exhaustive reports, the most complete and accurate being that of Nagashima, whose work, however, was based on a study of material procured at autopsy and from museum specimens.

The practitioner who is not acquainted with the gross pathology of this vaginitis may be perplexed when he first discovers it, and he will be astonished when he tries to perform a biopsy on the vagina only to have these apparent "nodules" break like so many toy balloons.

We wish to report the following case of vaginitis emphysematosa as our findings differ slightly from those reported in the literature:

Mrs. M. K., aged forty-two, was born in Lithuania in 1889. She had two children, both living and well. The patient was admitted to the hospital on Sept. 21, 1931,

complaining chiefly of nausea and severe epigastric pain. The last menses occurred July 20, 1931. At this time the vaginal mucosa was normal in every respect, no vaginal discharge was present and the fundus of the uterus was slightly enlarged.

Roentgenograms revealed considerable retention of barium after six hours and showed that a gastroenterostomy performed ten years previously had apparently closed.

The Aschheim-Zondek test (Friedman Modification) on Sept. 26, 1931, indicated that the patient was pregnant, and she was sent home from the hospital the same day. Because of the increasing severity of the epigastric pain she was again admitted Oct. 1, 1931, and a second gastroenterostomy was performed by the attending surgeon the following day, which almost immediately relieved her. She had not vomited at any time during her stay in the hospital.

On Oct. 15, 1931, the patient began to have a dark brown vaginal discharge, resembling a mixture of blood and amniotic fluid, and upon examination of the



Fig. 1.

Fig. 1.—The thin epithelial covering of a superficial nodule apparently lifted from the tunica propria. Magnification 130X.

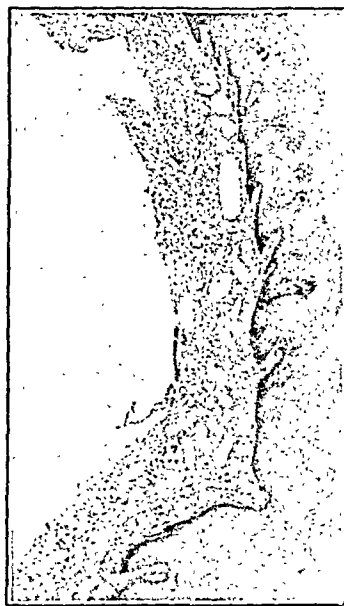


Fig. 2.

Fig. 2.—Dilated lymph spaces in the tunica propria. Magnification 100X.

vagina many very hard, small "nodules" were felt projecting slightly from the mucosa. No crepitation, as described by some authors, was elicited. The cervix was not dilated and the uterus was enlarged to the size of an eight weeks' gestation. A biopsy of the vaginal mucosa was performed on October 22, but unfortunately no cultures were taken at this time. Most of the "nodules" were found to contain gas under pressure and ruptured with a slight hissing sound if pressed very slightly. They were present throughout the vagina except near the external os, and varied grossly from about 1 mm. to 1.2 cm. in diameter. Only two or three of the larger gas "bubbles" were ruptured and no fluid was seen exuding therefrom. Their external walls were very tense and thin. The vaginal mucosa was not edematous and no hemorrhagic areas were seen.

An alkaline douche was the only treatment used at any time. On November 1, all of these lesions had disappeared, leaving a few very small, red, punctate areas in the upper half of the vagina. The patient aborted on Nov. 7, 1931.

## HISTOLOGIC EXAMINATION

Microscopically, many of the blebs or nodules on the vaginal mucosa had collapsed due to manipulation. Those that remained were rounded or sausage-shaped, varying in size from microscopic to 3 mm. in diameter and were found between the tunica propria and the epidermis and deeper in the connective tissue of the tunica (Fig. 1).

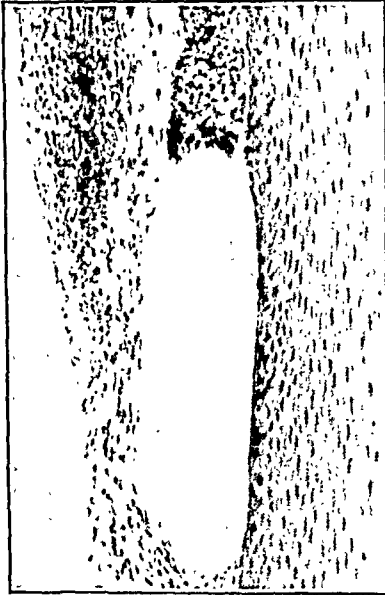


Fig. 3.



Fig. 4.

Fig. 3.—Dilated space in the tunica propria close to the epidermis. There is no endothelial lining and the space is occupied at one end by polymorphonuclear leucocytes. Leucocytes are also present in the surrounding tunica. Magnification 450X.

Fig. 4.—Islands of epithelium in the tunica propria, evidently infoldings of the surface epithelium. There is a diffuse infiltration with small round cells and polymorphonuclear leucocytes. Magnification 100X.

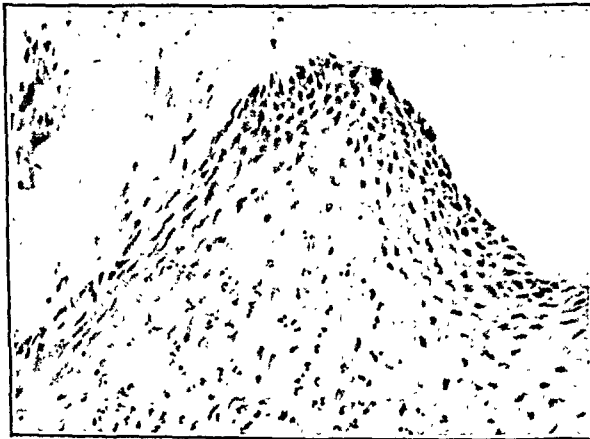


Fig. 5.—Portion of one of the epithelial islands showing polymorphonuclear leucocytic infiltration. Magnification 700X.

Some of the spaces had a single flattened cell lining while in others no such structure could be seen. Some of those showing a lining contained a pale pink, very finely granular or homogeneous substance evidently lymph, while spaces having no lining did not contain lymph but occasionally had masses of polymorphonuclear cells at one side with a smooth concave surface toward the lumen of the space as though pushed aside by gas or fluid (Figs. 2 and 3). There was also, contrary to the observations of

others, marked diffuse infiltration of polymorphonuclear leucocytes in the tunica propria and even in the squamous epithelium (Fig. 5). The vaginal epithelium was thrown into folds in places, and in others it was raised by the underlying cystic spaces. In the latter areas the cells were atrophic and decreased in number, and there was absence of rete pegs, while in the region of the infoldings there was marked hyperplasia and hypertrophy. No rete pegs showing central softening as described in the literature could be found in our sections. There were, however, numerous, rather large, detached islands of stratified squamous epithelium immediately beneath the mucosa or separated from it by a thin layer of connective tissue, evidently cut from infoldings (Fig. 4). In these islands, the cells were edematous and showed hydropic degeneration, but there was no further microscopic evidence to indicate that the islands had anything to do with the condition. They probably correspond to the cell nests described by Nagashima and Nowicki. The tissue was rich in engorged capillaries, many of which were found in the papillary tufts of the corium and, cut obliquely, gave a false impression of being in the germinal layer of the mucosa. There was moderate interstitial hemorrhage between the epidermis and tunica, and in this area the lymphatics were brought into prominence by virtue of great dilatation. No giant or multinuclear cells as described by others were noted nor were glandular structures and lymph follicles found.

Sections stained by the Gram-Weigert method showed many gram-positive cocci, all deep in the tunica propria and in relation to the areas of acute inflammation, but none were found in the cystic spaces and in the epithelium. No bacilli were found.

#### DISCUSSION

We believe the etiology of this condition is not entirely proved as yet. Lindenthal, who has made the most careful bacteriologic studies so far, obtained his material from a case diagnosed as "*peritonitis purulenta diffusa post endometritidem suppurativam (Partus); emphysema vaginalis; emphysema pulmonum*," at autopsy. He found large gram-positive bacilli with rounded ends on the mucosa of the vagina and cocci in pairs and chains. No microorganisms were seen in preparations from the interior of the "blister," but the material removed from them gave rise to growth on medium when anaerobic methods were used. Subcutaneous injection of these bacilli into guinea pigs and mice was followed by hemorrhagic edema with gas formation. He called this organism bacillus emphysematis vaginalis. We believe that Lindenthal may have been dealing with a bacillus of the Welch group.

Eisenlohr found small oval cocci in the capillaries and interstitial tissues. These microorganisms produced gas in a gelatin stab culture and in agar without free oxygen. Inoculation of these bacteria into the mucosa of the vagina and of the rectum of rabbits and guinea pigs was without significant results. Several other observers have found bacilli and some have found cocci in tissues removed from the vagina.

Many of the cases reported in the literature were patients who had remained in bed for a period of time before the disease developed. We believe that this probably prevented the entrance of much air into the vagina, thus favoring the growth of anaerobic organisms.

The assistance of Dr. J. J. Cunningham who performed the biopsy and operated on the patient is gratefully acknowledged.

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## UTERUS BICORNIS UNICOLLIS; HEMATOMETRA IN ONE HORN

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CONGENITAL malformations of the uterus are encountered with sufficient frequency to require no special comment, but when associated with complicating factors introducing problems of differential diagnosis, merit detailed report.

H. B., a girl twelve years old, was admitted to the hospital on June 20, 1932, for acute appendicitis. This diagnosis was made on the basis of pain in the right lower abdominal quadrant associated with nausea and vomiting for three days previous to admission. There was tenderness and rigidity in the right lower quadrant at the time.

Examination on the following day showed no clinical evidence of acute appendicitis. A large palpable sigmoid colon was thought to be due to fecal impaction. She was kept under observation, and as all symptoms subsided was discharged on June 24, 1932, without operation.

She was readmitted to the hospital on Sept. 24, 1932, with the following story. She felt well until Tuesday, Sept. 20, 1932, when her menstrual period began. She had cramps in the lower abdomen on Wednesday. Thursday she became nauseated and vomited watery material. Friday several enemas were given with poor results. Admitted to the hospital on Saturday.

Menstruation began eight months previously, at twenty-one to thirty-two-day intervals, lasting from four to six days. The flow was always accompanied by pain beginning on the second day and lasting one day or through the period.

Abdominal examination showed slight tenderness in right lower abdomen in the neighborhood of a marble-sized mass. No other abdominal tenderness, rigidity, or rebound.

Pelvic examination showed the hymen readily dilatable and admitted one finger without the slightest difficulty or traumatization. No cervix was at first palpable. On more careful palpation a small opening was felt flush with the anterior wall of the vagina. Immediately above this opening a mass, probably the corpus of the uterus, bulged sharply into the anterior wall, extending toward the left and up to within 1 inch of the umbilicus. The mass felt tense, yet elastic and smooth. To the right of this mass and near its upper part a firmer, smaller mass was palpable.

Blood examination showed 4,850,000 R.B.C., 62 per cent Hg, 9,600 W.B.C., and 74 per cent polymorphonuclears.

*Diagnosis:* Hematometra, probably in a bicornuate uterus.

Operation was performed on Sept. 27, 1932. The cervix was exposed. The external os was found in the anterior vaginal wall as a small dimple flush with the wall. The anterior lip was grasped by tenaculum. A sound introduced passed to the right of the bulging mass for a distance of about 4 inches. It was impossible to introduce the sound into the mass. An aspirating needle was introduced through the cervical canal and plunged into the large boggy pelvic mass. Aspiration withdrew dark, tarry, tenacious, bloody fluid. A large trocar and cannula was then introduced along the needle tract and about 10 ounces of this same material evacuated through the trocar. The trocar was withdrawn and the opening thus produced was gradually dilated to about  $\frac{3}{4}$  inch in diameter. The walls of the corpus were lightly curetted and the cavity was dried by iodoform gauze strip. A small cellophane wick drain was placed into the uterine cavity, the end protruding from the cervix. The vagina was packed with iodoform gauze.

The abdomen was then opened. The omentum was covered with dark, bloody fluid. A moderate quantity of similar tarry fluid was free in the peritoneal cavity. This was mopped up. After packing away the intestines, two uterine corpora were noted, each one well developed. Attached to the outer end of each corpus was one tube and ovary. The tubes on both sides were patent. The tube on the left side was distended, dark, and cyanotic. From the free fimbriated end of the left tube escaped the thin tarry secretion found in the uterine cavity. The ovaries were somewhat enlarged, white, and contained small cysts.

The cleft between the two corpora, which extended down to the internal os on the peritoneal surface, was covered with bloody plastic exudate. There was no indication for the removal of either uterine corpus or the adnexa.

The appendix was congested, elongated and tortuous, and was removed. The abdomen was closed in layers. The subsequent postoperative course was uneventful except for a rise of temperature to 101.2° F. on the fourth postoperative day. The wound healed by primary union and the patient was discharged on Oct. 11, 1932.

The patient was seen one year later. The menstrual history had been normal, free from pain. There was no evidence of the hematometra appreciable on pelvic examination. The ovaries appeared normal. An x-ray following the injection of Neo-Iopax into both uterine corpora showed both sides equal in size and both tubes patent.

This case is of interest not so much for the presence of a malformation of the uterus as for the complication accompanying this condition and the confusion in diagnosis resulting therefrom.

It will also be of interest to note whether some time in the future this patient will develop an endometriosis.

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Consoli, Vito: Influence of Experimental Hyperglycemia on the Female Genitalia. Clin. obstet. 11: 577, 1933.

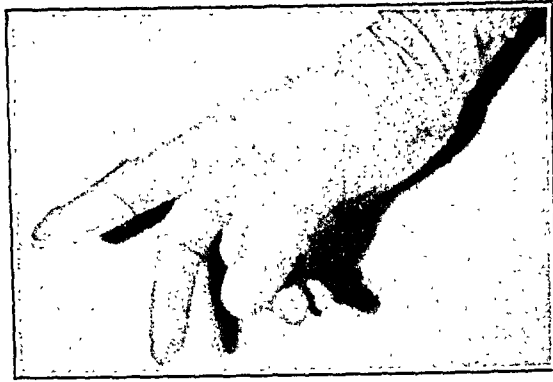
Experimental hyperglycemia, induced in rabbits either by pancreatectomy or by the subcutaneous injection of glucose, permitted the author to draw the following conclusions: (1) The experimental diabetes produces an atrophy of the ovary that involves both the germinal and the glandular portions. (2) The atrophic process extends to the uterus. (3) The external genitalia undergo the same changes. (4) The induced sterility is not due to the atrophic changes, but rather to the abrupt arrest of the ovarian function.

AUGUST F. DARO.

## A DEVICE FOR THE RUPTURE OF MEMBRANES

I. GEORGE WILTROUT, M.D., OSLO, MINN.

SOME time ago there was an article published suggesting the use of a thimble with a cut pointed end for the rupturing of membranes. Such I have tried but found impracticable by reason of the fact it will not stay on a slippery gloved finger. I have devised a little apparatus which is vastly superior and has served me well in over forty cases.



I have taken the finger tip aluminum splint made by the DePuy Manufacturing Co., have soldered on the tip a spear-shaped piece of sheet copper, narrowed the bridge at the tip and partially cut off the flexor tip to give a greater range of motion to the finger. All sharp edges have been smoothed off on the emery wheel.

The splint can be bent to hug tightly the finger before use so there can be no slipping off. I wear it on my right forefinger—using the index finger as a guide and as protection to the barbed point. I have never found anything quite as satisfactory for rupturing membranes.

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Novak, E.: Granulosa-Cell Carcinoma of Ovary as a Cause of Post Menopausal Bleeding, *Am. J. Surg.* 24: 595, 1934.

A cause of postmenopausal hemorrhage not generally recognized by surgeons and pathologists is the granulosa-cell carcinoma of the ovary. While rather rare, this tumor is of great biologic interest, particularly because the tumor cells produce folliculin, and thereby, in the postmenopausal patient, bring about a form of rejuvenation of the uterus. Periodic bleeding is reestablished and the uterus is often larger than its premenopausal size. Hyperplasia of the endometrium is noted in these patients. When well-marked hyperplasia of endometrium is revealed by diagnostic curettage, in cases of bleeding in elderly women, there should be strong suspicion of a granulosa-cell ovarian tumor. If a tumor can be palpated, the suspicion becomes almost a certainty. The possibility of luteinlike transformation of the granulosa cell of the tumor is discussed as a possible explanation of the secretory changes seen in some of the endometrial glands.

J. THORNWELL WITHERSPOON.

## Special Article

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### THOMAS CHALKLEY JAMES, A PIONEER IN THE TEACHING OF OBSTETRICS IN AMERICA

HERBERT THOMS, M.D., NEW HAVEN, CONN.

THOMAS CHALKLEY JAMES should interest American obstetricians because of the important rôle he played in the development of obstetric teaching in this country. The accounts of his life are meager, and the parsimony of his pen is indeed striking, but from that material which is available, his importance as a pioneer in American obstetrics is easily discernible. Thomas Chalkley James was born



in Philadelphia, August 31, 1776, the son of Abel James, "an active and successful merchant" of that city. His mother was the daughter of Thomas Chalkley, a minister in the Society of Friends. Both branches of his family originated in England and were connected with the Society of Friends. His father deserves more than a nominal mention, for his service to the cause of American liberty, although a noncombatant, was notable. He advanced money to Robert Morris, the head of the Committee on Finance, at a time when it was sorely needed. He was a friend of Benjamin Franklin, a member of the American Philosophical Society, and is said to have possessed one of the best



libraries in this country. We may believe that it was in an atmosphere of refinement and culture that Thomas James grew to manhood.

His classical education was chiefly gained at the Friends' Academy then presided over by Robert Proud, known to us chiefly because of his *History of Pennsylvania*. Proud was an Englishman, a member of the Society of Friends and a kinsman of Dr. John Fothergill. He had been educated for the medical profession but never went into practice and emigrated to this country in 1759. Two years later he became teacher of Greek and Latin at the Friends' Academy. A biographer states "he was never calculated for the storms and turmoils of life, but rather for the retirement of the academic grove, in converse with Plato, Seneca, Socrates, and other ancient worthies."

Following his course at the Academy, James began his medical studies under Adam Kuhn, the pupil and friend of Linneas and Professor of the Practice of Medicine at the University of Pennsylvania. The original plan was to secure his medical degree in Europe but financial reverses prevented this and he entered the University of Pennsylvania, graduating in 1787 as a Bachelor of Medicine. The next year through the influence of friends he procured the office as surgeon in a mercantile vessel, the "Sampson," bound for the Cape of Good Hope and Canton. A voyage of that magnitude in the sailing vessels of that day certainly stimulates our imagination in spite of a biographic note that states that the "voyage was productive of no remarkable incidence, but gave opportunity for reading and reflection." It was this voyage that furnished James the means for furthering his medical career, for it is said that "by a judicious mercantile adventure" he procured the necessary funds. In 1791 he went to London where he found his fellow-townsmen, Philip Seng Physick, then a pupil of John Hunter at St. George's Hospital. It was through Physick's efforts that he entered (May 30, 1791) as a house pupil in the Store Street Lying-In Hospital then under the direction of William Osborn and John Clarke. During the winter of 1791-92 he remained at London and in the spring of 1792 went to Edinburgh in company with David Hosack of New York and John Ruan of Philadelphia. After spending a year at Edinburgh, where it does not appear that he graduated, he sailed for America with Ruan, arriving at Wiscasset, Maine, in June, 1793. He came home in time to aid in combating the devastations of the plague which was then epidemic in Philadelphia. In appreciation of his efforts during that time he was, at a later date, presented with a handsome piece of plate by the Welsh Society of Philadelphia.

Thomas James first comes to our notice as a teacher of obstetrics in 1802 when on November 17 of that year in conjunction with John Church he gave a private course of lectures which was attended by 20 pupils. This is said to have been the first regular and consistent

effort to teach obstetrics in this country, although Shippen and Dewees had both lectured previous to this time. The former gave obstetric lectures in connection with his course in anatomy, while the latter had made a not too successful attempt to give private lectures. It is therefore probable that to James and Church belong the credit for the first complete course of lectures on this subject given in this country. It was not long before they wished to add practical instruction to the curriculum and they finally succeeded in having a lying-in ward established in the Alms House. It was agreed that they would attend this ward and that they should have a certain number of pupils present at each case of labor. In 1805 we find that tickets for instruction at the Alms House were issued at \$8.00. The importance and extent of clinical instruction at that institution is shown by the fact that within ten years, between 1815 and 1825, \$11,160.00 had been collected as fees.

In the year 1808, William Shippen, Professor of Anatomy and Midwifery, died, and Caspar Wistar was chosen as his successor. The new occupant of the Chair urged upon the trustees of the university the necessity of a separate Chair for midwifery, but two years elapsed before final action was taken. On April 10, 1810, we find a resolution adopted by that body stating, "that the present establishment of a Professor of Anatomy and Midwifery be divided, and that hereafter there shall be a Professorship of Anatomy and a Professorship of Midwifery, but it shall not be necessary in order to obtain the degree of Doctor of Medicine, that the students shall attend the Professor of Midwifery." The fact cannot be concealed that with the establishment of the new Chair the elevation of obstetrics to an independent position was not generously given. This is particularly shown by the fact that attendance upon lectures in that subject was not obligatory for obtaining the degree.

Although there were several candidates for the new position including William P. Dewees and Nathaniel Chapman, in 1810 James was elected, to be assisted by Chapman. His first course of university lectures was given in November of that year and at the next commencement his Alma Mater conferred upon him the Honorary Degree of Doctor of Medicine. In 1813 Benjamin Smith Barton was called to the Chair of Medicine made vacant by the death of Benjamin Rush, and Nathaniel Chapman went to the Chair of Therapeutics and Materia Medica, leaving James the sole occupant of the Chair of Midwifery. It was in the next year that James made probably his most important written contribution to obstetrics. This appears in the *Electric Repository* for 1811 and is entitled "Case of Premature Labor Artificially Induced."

The induction of premature labor in cases of contracted pelves is said to have originated as a method of treatment at a meeting of London obstetricians in 1756. However, we are chiefly indebted to

Thomas Denman for its acceptance as a recognized procedure. His advocacy of the operation in his *Introduction to the Practice of Midwifery*, published in 1801, brought the matter to general consideration. This treatise, which has been called by Spencer "the most splendid work on midwifery in the English language," had great influence in America at a time when the writing of textbooks in medicine on this side of the Atlantic was practically nonexistent. Thomas James was not only well acquainted with Denman's work, but probably had a personal acquaintance with him during his sojourn in London. His description of the procedure is an excellent example of the medical writing of that period as some of the passages here transcribed will testify.

He writes:

Upon our opinion being requested we again agreed to state, that our patient probably never will bear a living child at the full period of uterogestation. We therefore advised, that if she should again find herself in that situation, she should adhere to an abstemious regimen, be occasionally bled, and from time to time take a cathartic; and that at the period of seven months from conception, premature labour should be induced by rupturing the membranes. . . . Dr. Mongez saw the patient from time to time, and informed me in the spring of the present year (1810) that she was again pregnant, and that both herself and her friends were anxious that the plan that we had proposed should be carried into effect. Not long after she called upon me, and appeared to be willing that the experiment should be tried. On the twenty-sixth of June, 1810, when, according to the most accurate account we could procure, she was at the end of the seventh month of pregnancy, we examined her per vaginam, and during the examination found the os uteri dilating to nearly the size of a half dollar, and that the oviform presentation of the membranes could be distinctly felt. As she was to be removed from Queen street, where she then dwelt, to her mother's house in Union, near Fourth, previously to rupturing the membranes, we contented ourselves with recommending venesection and an enema for the present. On the twenty-seventh in the morning she was removed to her mother's, and on the evening of that day I was informed by Dr. Mongez that the membranes had spontaneously ruptured with very little pain. (Footnote: This spontaneous rupture, if it may be so termed, must be attributed to the irritation produced by the examination made the day preceding, Dr. Mongez having then, as he informed me, after the partial irritation of the os uteri, endeavored to scratch the membranes with the nail of his forefinger. Hence contraction of the uterus must have been in a degree produced, and the rupture of the membranes necessarily facilitated.)

On the twenty-ninth in the morning, about 8 o'clock, I was requested by the husband to meet Dr. Mongez at her mother's house, which I accordingly did. We found that labour had commenced, and upon examination, about half past 9 A.M. the os uteri was found to be considerably dilated, so that the presentation could be clearly distinguished, the posterior fontanelle being towards the left acetabulum. We agreed, as there were no reasons to justify precipitation, to suffer the labour to proceed, and by about half past 10 A.M. she was delivered of a living female child, which, as we had previously calculated, appeared to be at the period of seven months from conception.

While the above essay is probably James's most important written contribution we should also mention his very excellent observations

on "Extrauterine Pregnancy" and on a "Case of Hydatids," both to be found in the *Transactions of the Philadelphia College of Physicians*.

James's chief biographer, Hugh L. Hodge, says that he was an excellent teacher and that his "lectures were handsomely and classically written." However, the same authority states that "his delivery was not very impassioned, he wanted more energy, and more vigour and voice in his composition." With regard to the latter statement it is highly probable that James's ill health was largely responsible, for in 1821 it was apparent that his physical strength was failing. At this time he applied for an assistant and four years later Dewees was appointed Adjunct Professor. However, he continued until 1834 in which year he resigned.

In reviewing the contributions to medicine of Thomas Chalkley James we should emphasize also his service to the Pennsylvania Hospital, first as Physician and then as Obstetrician, and to the Philadelphia College of Physicians which he served as secretary six years, treasurer seventeen years, vice-president and, in 1835, president.

It is a fact that in many biographies of medical men, so much emphasis is placed upon the medical aspect of their careers that often a very essential part of the portrait remains wanting. The extra medical activities of men like Benjamin Rush or Joseph Warren form indeed an important part of their biography. In Thomas Chalkley James we find not only a fine citizen, but also a distinct force in the civic affairs of his day. As early as 1794 we find him accompanying the "MacPherson Blues" as Surgeon, in a western expedition to suppress the disturbance known as the "Whiskey Insurrection." During this occasion James is said to have written a song at a time when great gloom had pervaded the corps and which had a fine effect upon the spirits of that organization. This body of men which had its inception in 1794 Watson says "surpassed all volunteer array in our city, both for numerical force and the respectability of the young men enrolled . . . for array discipline and exercise were the *Lions* of that day, and won golden opinions readily from all." We should perhaps add that the author of these lines was himself a member of the troop.

In the early part of James's life he was interested in belles lettres and anonymously wrote poetry for some of the magazines of that day. Under the signature of P. D. he is said to have published in the *Portfolio* for 1801 a versified translation of the *Idylls of Gesner* which showed his knowledge of the German language. He was also much interested in matters of local history and it was almost entirely by James's influence that the Pennsylvania Historical Society was founded. Like his father he was a member of the American Philosophical Society, at one time acting as secretary. In the field of medical publication he was active as an editor of the *Elcctic Repository*. He also

edited an American edition of Burns's *Principles of Midwifery*. His scholarly attainments are shown by his interest in the Bible "not only in his native language but also in the original Hebrew and Greek, and in the Latin, French and German versions."

The closing years of James's life seem to have been those of quietness and retirement in which he avoided social meetings and devoted his time to reading and study. On July 5, 1835, he died. In reviewing his life we are impressed with his usefulness as a man, his great devotion to high medical ideals, and his important place in the real beginnings of obstetric teaching in America. His biographer and a successor in the Chair of Obstetrics, Hugh L. Hodge, describes him when "some fifty years had passed over his head. . . . He was partially bald, his hair whitened, and his form so originally perfect was now somewhat bent, but his ruddy and healthy aspect, his fine countenance, his diffident yet refined manners, his affability, his condescension to medical students, his great intellectual and moral worth, excited feelings of affection and veneration in the minds and hearts of all."

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**Burger, P.**: *Pregnancy After Intrauterine Application of Radium*, Bull. Soc. d'obst. et de gynec., p. 386, 1934.

Burger reports two cases of pregnancy subsequent to intrauterine radium treatment. Pregnancy after irradiation is not a rarity; Flascamp collected a series of 133 gestations in 117 women who had been irradiated with roentgen rays, and 54 pregnancies among 46 women treated with radium. It is well known that infants born after irradiation which was given during pregnancy, are frequently deformed. The nervous system in particular is defective. On the other hand, in the cases where the irradiation was carried out in the nonpregnant state, the children born after such treatment are nearly always normal. In Flascamp's series all the babies were healthy. However, some authors basing their opinion on animal experimentation maintain that such babies may be born with malformations, even though they appear normal. They may be damaged and transmit their defects to their children.

J. P. GREENHILL.

# Department of Book Reviews

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CONDUCTED BY ROBERT T. FRANK

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## Review of New Books

### Gynecology

The author of this book, *Human Sterility*,<sup>1</sup> has been for some years Chairman for Sterility on the National Committee on Maternal Health, and the book is published under their auspices. In his clinical work on sterility he has adopted the group study of the infertile mating, having associated with him an internist, a urologist, and an endocrinologist, who have collaborated also in the preparation of the text. The result is a very competent and timely presentation of the present facts regarding the diagnosis and treatment of sterility.

In the section on the causation of human infertility the functional and organic lesions of the male and female organs are taken up with a tabular presentation of the incidence and distribution in a series of 100 cases which were completely studied by the group method. The diagnostic study of the sterile mating presents a well-developed scheme through examination, by clinical, physical, urologic, gynecologic, and laboratory procedures of the partners. Clinical methods are described in detail, and there is an evaluation of the various findings by laboratory tests. The indications for treatment are clearly explained, the limitations of surgery are closely defined, and the need for continued oversight of the patient under certain lines of treatment is stressed.

Of particular interest in view of the newer developments in physiology in recent years is the author's attitude toward endocrinologic diagnosis and treatment. The diagnosis of the endocrinologic causative factors is made by history and examinations. The suggestive items are summarized as to frequency and importance, in table form under three parallel headings, pituitary, thyroid, and ovary. In a similar manner are tabulated the findings from the laboratory tests which are at present believed to indicate deviations from the normal in the activity of these three glands. The author believes that only hypofunctions of these glands are of moment in clinical cases of sterility. His caution in the interpretation of these findings is admirable, and is equalled by his judicious restraint in the handling of endocrine treatment of sterility. In this respect he regards such treatment of each patient as an individual experiment, and questions whether the newer follicular and estrous-producing hormones can actually stimulate normal ovulation.

This is a very complete presentation of the present knowledge of the subject, ably handled, and is an excellent working manual in the detail of methods and their evaluation.

—Philip F. Williams

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<sup>1</sup>*Human Sterility, Causation, Diagnosis and Treatment.* By Samuel Raynor Meaker, Professor of Gynecology, Boston University School of Medicine. Pages 264, with 27 illustrations. The Williams & Wilkins Company, Baltimore, 1934.

The second edition of Curtis' book, *A Textbook of Gynecology*,<sup>2</sup> shows careful revision. This textbook is short, well conceived, and well carried out. It saves the student from mulling over many pages of text because of its conciseness and the weighing of every word. The illustrations, as in the previous edition, are excellent, well chosen and artistic.

I would suggest that in future edition, x-ray as a treatment of fibroids should at least be mentioned, as in many ways it obviates the objections which the author voices as features of radium application. Considering the importance that endocrinology plays in gynecology of today, this chapter will bear amplification and clarification.

Fig. 29, which shows the reopening of the abdominal end of the tube by stretching with scissors, applies to so few cases that it might well be omitted. Fig. 65, in which the technic of supravaginal hysterectomy is illustrated, might be improved by showing the bladder pushed down rather than applying clamps after section of the peritoneum.

On the whole, this is one of the best short textbooks accessible to the American student.

—R. T. Frank

This is a very fine single volume exposition of gynecology, *The Principles of Gynaecology*.<sup>3</sup> In the present edition attention has been paid to the changing concepts of pelvic physiology and the various interdependencies of the glands of internal secretion. There have been added a short historical introduction, and noteworthy sections on the ethical and medicolegal questions frequently arising in gynecologic practice.

Realizing the inseparability of obstetrics and gynecology the author has included much material essential to both subjects, for instance, a chapter on therapeutic abortion, for which he seems to feel liberal indications. Appreciating, too, the changing social and economic conditions, although limiting himself to the medical indications, he brings in a sane discussion of contraception. In the conclusion of disorders of the menopause appears the naïve statement that "Kraurosis, is, however, often confused, especially in the United States, with leucoplakia vulvae."

In the discussion of malignancy appears an excellent critique on radium, which the author feels will sooner or later be supplanted by other physical agents or measures. Of especial interest is the present and favorable opinion of the author in regard to the treatment of cancer with lead. The operation of salpingectomy with acrohysterectomy, often referred to as the Bell-Beutner operation, is beautifully illustrated.

The present edition is enriched with over 100 new illustrations and many beautiful color plates, and a large number of well-executed photomicrographs. The main section of the book, which should be of assistance to the student and general practitioner, is an etiologic classification of symptoms and manifestations. The revision and rewriting of the book keeps it on a very high plane.

—Philip F. Williams

Knaus's thesis, *Die Periodische Fruchtbarkeit und Unfruchtbarkeit des Weibes*,<sup>4</sup> is the periodic fertility and infertility of women. In the elaboration of this thesis

<sup>2</sup>A Textbook of Gynecology. By Arthur Hale Curtis. Ed. 2, reset, with 300 original illustrations, chiefly by Tom Jones. W. B. Saunders Co., Philadelphia, 1934.

<sup>3</sup>The Principles of Gynaecology. By William Blair-Bell, Emeritus-Professor of Obstetrics and Gynaecology in The University of Liverpool. Revised and largely rewritten with the assistance of M. M. Datnow and Arthur C. H. Bell. Fourth Edition. With 507 illustrations. William Wood and Co., Baltimore, 1934.

<sup>4</sup>Die Periodische Fruchtbarkeit und Unfruchtbarkeit des Weibes. Der Weg zur natürlichen Geburtenregelung, von Professor Dr. Hermann Knaus. Verlag von Wilhelm Maudrich. Wien, 1934.

he gives an excellent review of the physiology of the female genital tract in both animals and human beings.

He reviews the work of Hartman on his monkey colonies in which 420 copulations resulted in 52 conceptions of which 49 fell between the eleventh and sixteenth day of the cycle. Knaus emphasizes the short duration of the receptivity of the ovum and likewise features the short period of sperm viability (forty-eight hours) within the female genital tract. The conclusions which he draws from the experiment, that the corpus luteum effect produces nonreactivity of the uterus to pituitrin, appear unwarranted. They simply serve to show a single corpus luteum reaction which is probably concomitant in time with the progestational endometrial changes. Incidentally he does not mention Leo Loeb either in the text or in the literature although Loeb's work was fundamental and particularly emphasized the inhibitory effect of the corpus luteum on follicle growth.

On the basis of the uterine contraction experiment, the author states that human ovulation occurs fifteen days after the menstruation. He states in a categorical fashion that fertility is limited to three days before and one day after ovulation has occurred.

While this monograph is important and of interest, it appears to add nothing to the much disputed question as to whether there is really a safe period in the human.\*

—R. T. Frank

In discussing the conservative methods useful in gynecologic practice Kahr, *Konservative Therapie der Frauenkrankheiten*,<sup>5</sup> brings out in a series of chapters on special topics, the medical and physical measures which may precede, correlate, or follow operative therapy. He has included chapters on enteroptosis, backaché, constipation, and the important diseases of the urinary tract. The book is replete with prescriptions, formulas, and schematic suggestions for treatment.

There is an excellent discussion of the endocrine relationships in the opening chapter on Amenorrhea. Kahr presents the various opinions expressed in recent literature as to the mode and value of hormone therapy in this condition, and feels that at best it is simply substitutional therapy in most instances. From the list of ovarian preparations mentioned, it is apparent ours is not the only country with busy biologic factories. In the section on Metrorrhagia, adult and juvenile, there is a further discussion of the endocrine system, and an extended review of the endocrine treatment of these bleedings.

Under Chronic Pelvic Peritonitis appears a discussion of the effects of heat variously derived and applied. The review of the literature indicates a favorable attitude toward vaccine therapy in chronic gonorrhea. Actino-therapy is described in the section on Tuberculosis. Radium and roentgen therapy are taken up at length in the chapter dealing with Carcinoma. In the palliative treatment of inoperable carcinoma he makes no suggestion as to pelvic sympathectomy for the relief of pain.

The limitations of medical treatment are generally discussed in the appropriate chapters together with the indications pointing to the need for surgical interference. Such a detailed exposition of conservative methods should make the book not only of value to the specialist but of even greater use to the general practitioner.

—Philip F. Williams

As the result of ten years of investigation Araya in this monograph, *Ovulation et Menstruation*,<sup>6</sup> reaches the conclusion that there is no relationship between ovula-

\*This volume now has appeared in an English translation.

<sup>5</sup>*Konservative Therapie der Frauenkrankheiten*. Von Dr. Heinrich Kahr, Privatdozent für Geburtshilfe und Gynäkologie an der Universität. Julius Springer, Wien, 1934.

<sup>6</sup>*Ovulation et Menstruation*. Rafael Araya. Libreria Medica Lagos. Rosario, Argentina.



tion and the ovular cycle, and menstruation and the menstrual cycle. The studies made consisted of the following: (1) 385 laparotomies performed for different conditions and at varying periods in the menstrual cycle, during which the ovaries were examined macroscopically; (2) 66 cases in which the corpus luteum was examined histologically; (3) 15 cases in which curettings were examined histologically; (4) 23 cases in which both curettage and laparotomy were performed and the curettings correlated with the ovarian cyclic findings; (5) 41 cases studied histologically from museum specimens.

The conclusions drawn are in direct variance with modern views regarding the relationship between a distinct ovular cycle and a distinct menstrual cycle. For example, he finds mature corpora lutea as well as ripe graafian follicles at almost any or every point in the menstrual cycle, and frequently complete absence of both. He does find, however, that ripe follicles are most frequently seen between the eleventh and fifteenth day of the menstrual cycle and that the mature corpora lutea are most frequently found between the twenty-first and the twenty-fifth day. His examination of curettings demonstrates that although the mucous membrane undergoes a distinct cycle, these cyclic changes are not related to menstruation per se. He also finds that the follicular ovarian cycle including the corpus luteum bears no relationship to the menstrual cycle including the cyclic mucous membrane changes.

As can be seen the views expressed are radical in the extreme. If they are to be accepted, our present conceptions regarding ovulation and menstruation must be completely set aside. His conclusions, however, cannot be accepted for the following reasons: First, the material studied is too small to serve as a basis for such sweeping statements. Second, his work is not exact as is evidenced by the fact that many of the microphotographs illustrating his conclusions have not been interpreted correctly. Third, he himself finds that in most cases the mature follicle and corpus luteum have a definite place in the menstrual cycle. Fourth, such conditions as require laparotomy may in themselves influence both ovarian and menstrual cycles so as to present an abnormal picture. Fifth, it must be emphasized that macroscopic examination of the ovaries in situ represents a poor method upon which to base conclusions.

It may be called to the author's attention that menstruation occurring without ovulation and vice versa is accepted by most authorities. When this occurs, however, it represents a distinct functional abnormality. Such an abnormality can frequently be demonstrated by hormonal studies.

—Frank Spielman

This memorial volume, *The Golden Book*,<sup>7</sup> is issued in honor of Professor Iribarne of the University of Buenos Aires who died in 1933. It represents the work either completed or in progress during his stewardship as head of the Gynecological Department of the University. It consists of some 24 articles on a variety of gynecologic subjects giving a fair cross-section of the field. The scope of the work can readily be comprehended by reference to such widely divergent subjects as endometriosis, the Wertheim operation, Paget's disease of the breast, the importance of radiography of the sella turcica in gynecology, ovarian tumors, results of curietherapy in carcinoma of the cervix, the neurotropic cells of the hilum of the ovary, etc., to mention only a few.

The chief protagonist of the work is Ahumada who has contributed or collaborated in all but three of the articles. Although most of the material is not new it is well presented and illustrated, and the bibliographies appended are in most cases exhaustive. Occasionally, as in the article, "Chronic Encapsulated Peritonitis from the Gynecological Standpoint," there are such extensive compilations of the litera-

<sup>7</sup>*Libro de Oro. Prof. Dr. Julio Iribarne, in Memoriam. Homenaje de sus Colaboradores y Discipulos de la Catedra de Clinica Ginecologica. Buenos Aires, 1934.*

ture that one cannot see the forest for the trees. Ahumada states in his preface that the entire book was compiled within a period of two months. This in itself makes its publication a remarkable feat.

—Frank Spielman

The history of castration, *Die Technik der Sterilisierung und Kastration*,<sup>8</sup> from the time of Semiramis to Hitler, the eugenic and sociopolitical indications and the technic of the operative measures for the sterilization of male and female form the subject matter of this small pamphlet. Boeminghaus gives the technic for castration and sterilization of the male, favoring resection of the vas deferens; while Naujoks describes the various procedures on the female, giving preference to the Madlener operation of crushing and ligation of the uterine tube. Hormonal injections and roentgen ray sterilization are summarily dismissed.

Such a résumé of methods of preventing reproduction no doubt will be found useful in the proposed program of mass sterilization to diminish inheritable disease in future generations in Germany.

—Philip F. Williams

### Obstetrics

Recent efforts to discover and eliminate certain causes of fetal and maternal mortality and of puerperal and infant morbidity have firmly established the important rôle played in this respect by complicating diseases. From this viewpoint a new volume entitled *Obstetric Medicine*<sup>9</sup> and dealing with the diagnosis and treatment of diseases more commonly encountered in pregnant women represents a timely contribution. In this volume known experts discuss the particular type of disease which most interests each, and point out the effects of the disease on the course of pregnancy and on the fetus together with possible influence of the coexisting pregnancy on the usual course of the disease.

Drs. Adair and Stieglitz, editing the many contributions from the standpoint of obstetrician and internist respectively and combining them into a thoroughly unified presentation of the entire problem, deserve credit for their excellent work. A complete index is appended.

—Hugo Ehrenfest

This book, *Postures and Practices During Labor Among Primitive Peoples*,<sup>10</sup> is an intriguing discussion of world-wide folklore of obstetrics, particularly parturition. Jarcho has collected the habits and manners of conducting labors in the ancient and modern backwaters of humanity, and it is rather surprising what similarities of curious practices existed in far separated peoples, and that a few of them exist, to some extent, today.

Of particular import is the chapter on Primitive Postures in Labor, the antecedents of the Walcher position, the abdominal binder, the Credé maneuver, etc. The illustrations have been collected from many sources, and one is impressed with the comparison of primitive and modern methods; for instance, the conduct of the third stage of labor as depicted in Figs. 75 and 76.

<sup>8</sup>*Die Technik der Sterilisierung und Kastration.* Von H. Naujoks, Oberarzt der Frauenklinik, and H. Boeminghaus, Oberarzt der Chirurgischen Klinik, Marburg/L. Mit 18 Abbildungen. Ferdinand Enke, Stuttgart, 1934.

<sup>9</sup>*Obstetric Medicine. The Diagnosis and Management of the Commoner Diseases in Relation to Pregnancy.* Edited by Fred L. Adair, M.D., Professor of Obstetrics and Gynecology, University of Chicago, and Edward J. Stieglitz, M.D., Assistant Clinical Professor of Medicine, Rush Medical College in Chicago. Illustrated. Lea & Febiger, Philadelphia, 1934.

<sup>10</sup>*Postures and Practices During Labor Among Primitive Peoples. Adaptations to Modern Obstetrics.* By Julius Jarcho. 154 pages, with 130 illustrations. Paul B. Hoeber, Inc., New York, 1934.

The use of urine; therapeutically, by the Chinese and others leads to some speculation as to their possible early discovery of the hormonal value of this excretion. The chapter on Anthropology is of practical value in relation to the cosmopolitan obstetric practice of eastern cities. Modern postures as aids in puerperal convalescence are described in the closing chapter. This comparative review of ethnological obstetric practice should be of interest to those engaged in obstetrics.

—Philip F. Williams

This is a book, *The Pregnant Woman*,<sup>11</sup> written for the laity dealing with the many perplexing problems that face the pregnant woman. Starting with the menstrual cycle the author discusses the problems of sex hygiene, contraception, pregnancy, the puerperium, and venereal diseases. A chapter is devoted to the subject of abortion stressing the moral issues and the dangers of infection. The body of the book deals in detail with the proper management of the pregnant woman during the various stages of pregnancy. A chapter is devoted to the care of the newborn infant. The book is written in a simple style with a minimum of medical terms. It contains much material that will be found both interesting and useful to the lay reader interested in the physiology of the female during pregnancy.

—U. J. Salmon

The practical aspects of midwifery are concisely and thoroughly presented in the seventh edition of this book *Midwifery for Nurses*.<sup>12</sup> Antenatal care, obstetric diagnosis and the conduct of labor are discussed in detail. The section dealing with the care of the infant has been revised. The simplicity of the manner of presentation and the numerous illustrations combine to make this a useful text.

—U. J. Salmon.

### Miscellaneous

Robson's monograph on *Recent Advances in Sex and Reproductive Physiology*<sup>13</sup> is an excellent, well-arranged and well-written summary of our present knowledge of the endocrine glands and their effect on the reproductive sphere.

The book contains a fund of information, clearly presented, and fully illustrated so that both the worker in these lines as well as the physician who tries to keep up with this constantly changing branch, will find it of use. Every chapter has a short but good bibliography by means of which reference to original sources is simplified. A surprising amount of information is contained within the 240 pages of this little book.

—R. T. Frank.

The seventh edition of Zinsser and Bayne-Jones' *Textbook on Bacteriology*<sup>14</sup> is a carefully edited and valuable treatise which as the authors say, in the first editions

<sup>11</sup>*The Pregnant Woman*. By Porter Brown, M.D., Eugenics Publishing Company, Inc., New York, 1933.

<sup>12</sup>*Midwifery for Nurses*. By Henry Russell Andrews, M.D., B.S. (Lond.), F.R.C.O.G., F.R.C.O. (Lond.), Consulting Obstetric Physician, London Hospital; Late Examiner in Midwifery and Diseases of Women to the Conjoint Board, The Universities of Oxford, Cambridge, Durham and London, and to the Society of Apothecaries; and Victor Lack, M.B., B.S. (Lond.), F.R.C.P., F.R.C.S. (Edin.), M.C.O.G., Assistant Obstetric and Gynecological Surgeon, London Hospital; Gynecologist, King George Hospital, Ilford; Assistant Examiner in Obstetrics to the University of London. Seventh Edition. William Wood and Company, Baltimore, 1934.

<sup>13</sup>*Recent Advances in Sex and Reproductive Physiology*. By J. M. Robson. With introduction by Prof. F. A. E. Crew, Philadelphia, P. Blakiston's Son & Co., Inc. 1934.

<sup>14</sup>*A Textbook of Bacteriology*. With a Section on Pathogenic Protozoa. By Hans Zinsser and Stanhope Bayne-Jones. Rewritten, revised and reset. With 174 illustrations in the text. Seventh Edition. D. Appleton-Century Co., New York, 1934.

designed merely to cover the fundamental laws and technic of bacteriology, has gradually developed in addition into a manual on infectious diseases, including their diagnosis, specific therapy, epidemiology and prevention. The importance of immunology in the study of protein chemistry and metabolism is becoming more important as time passes. Viruses are assuming such major proportions that eventually they will require a separate treatise.

In order to cover the immense amount of detail necessary in a book of this type, all technical details have been relegated to the end of the volume. In the text, such new developments which have been published in the early part of 1934, have been incorporated.

The authors take an extremely conservative stand which adds to the value of the book. At present they say a classification of *Streptococcus scarlatinae* "is not warranted" nor has a specific type of hemolytic streptococcus which produces puerperal sepsis been demonstrated. Gonococcus vaccine therapy, while promising, is by no means convincing. Passive immunization by means of animal serum does not permit of their final judgment.

While the book covers an extremely broad field, certain omission may be mentioned. The Frei test for lymphogranuloma inguinale is not spoken of. The Schwartzman phenomenon is likewise not mentioned.

—R. T. Frank.

The use and limitations of spinal anesthesia in obstetrics and gynecology are subjected to a critical analysis in this book, *Lumbalanästhesie in der Geburtshilfe und Gynäkologie*.<sup>15</sup> The author has found the method of great value in his gynecologic operations, particularly in such prolonged abdominal procedures as the radical hysterectomy for carcinoma. The statistics quoted are extremely favorable. On the other hand the author freely admits the disadvantages and limitations of the method in obstetric practice. He realizes that the short duration of this method of anesthesia precludes its substitution for other forms of analgesia-anesthesia during labor. He feels it has a special field in operating in the toxemias with high blood pressure, and that it may be used for all obstetric operations, especially cesarean section, except in the face of grave cardiac disease or severe anemias. He finds no increase of hemorrhage following its use. Although he prefers the sitting position for the administration of the agent in gynecologic practice, he finds no technical difficulties added by the necessary side position used in obstetrics. The author warns particularly against the use of morphine and scopolamine in conjunction with spinal anesthesia. The general basic principles of spinal anesthesia, history, biochemistry of the fluid, technic, and influence of the agents and method on the intermediary metabolism are thoroughly discussed in appropriate chapters. The author has stressed especially the limitations and contraindications of this method.

—Philip F. Williams.

To every woman who cares about the way she looks, and the way she feels as she moves about the world, we recommend *Your Carriage, Madam!*<sup>16</sup> by Janet Lane. Every physician who realizes the tremendous importance of correct carriage in women's health, and, moreover, every physician who deplores the effect of unwise dieting in the attempt to rectify the defects in carriage and figure, should recommend this book to his patients.

<sup>15</sup>*Lumbalanästhesie in der Geburtshilfe und Gynäkologie*. Mit besonderer Berücksichtigung der Biochemie des Liquors und der Blutliquorschranke. Von Ernst Preissecker. Assistent der II. Univ.-Frauenklinik, Wien. Mit einem Vorwort von Prof. Dr. W. Weibel. 74 Pages, Mit 2 Abbildungen und 3 farbigen Tafeln. Wilhelm Maudrich, Wien, 1934.

<sup>16</sup>*Your Carriage, Madam! A Guide to Good Posture*. By Janet Lane. New York, John Wiley & Sons, Inc. 1934.

The author of this "guide to good posture," is supervisor of corrective exercise at the Obesity Clinic of the University and Bellevue Hospital Medical School, New York University. Experience has convinced her of the direct relationship between correct carriage and correct contours, an idea which makes a far stronger appeal to the feminine mind than any direct linking up of either of these factors to health itself. With delightful humor, simplicity, and common sense she describes, first, the natural structure of the body, and second, the way in which this structure can most efficiently, easily, and gracefully be used.

It is not a book of exercises, to be gone through every day, but a book that tells the reader how to exercise her body all day long in everything she does—how to make housework, walking, typewriting, driving a car, even sitting at the movies, an exercise of grace.

—K. L. Kosmak.

The title of this volume of 283 pages, *Genealogy of Sex*,<sup>17</sup> is well chosen since it presents a fairly complete survey of the evolution of sex function all through animal life from the unicellular ameba up to man itself. One cannot fail to be impressed with the skill of the author in packing such a wealth of interesting scientific information in regard to the behavior of animals of all kind, insect, fish, bird, reptile, mammal, incident to reproductive activity, within the confines of just one readable volume of moderate size. Unable to outline the rich contents of this book we wish to inform the gynecologist that he can find in it, e.g., the detailed description of at least two methods of artificial insemination as routinely practiced by certain insects, or of the actual change of the one sex into the other for the purpose of meeting certain exigencies. The last chapter, entitled "Love in Human Beings," probably is the least interesting but we suspect has prompted the publishers to create the regrettable impression that they are offering one more of those "instructive sex books" which now under protection of certain court decisions can be widely distributed for the "benefit" of the reading lay public.

—Hugo Ehrenfest.

Cetroni and Azzariti: Intrauterine Photography, Clin. obstet. 11: 449, 1933.

The authors have studied x-ray plates of the pregnant uterus, from the seventh to the ninth month, in 25 women, following the injection into the amniotic sac of opaque substances through the abdominal wall. Excellent results were obtained with uroselectan, 30 to 40 c.c. No maternal or fetal harm was observed.

The x-ray plates, above all, show the outline of the fetus including the small parts. The sex of the fetus can almost always be differentiated. The cord is very plainly seen about the neck or extremities of the fetus. The placental site can be located. The fetal movements can be observed. The rapid passage of the amniotic fluid into stomach and intestines can be followed.

In two cases in which the opaque substance was injected during labor, the placentas were x-rayed after expulsion. The plates clearly illustrated the vascular system of the placenta. This proves that the opaque substance passes into the fetal circulation.

AUGUST F. DARO.

<sup>17</sup>*Genealogy of Sex.* By Curt Thesing, M.D. Translated from the German. New York, Emerson Books, Inc., 1934.

## Selected Abstracts

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### Labor

Frey and Wenner: The Crodel Method of Measuring Labor Pains, *Arch. f. Gynäk.* 152: 447, 1933.

The authors used Crodel's apparatus for measuring labor pains. This consists of a tonometer-like apparatus by means of which the force of an individual uterine contraction can be measured and the working capacity of the uterus estimated.

Studies made on 28 women in labor failed to confirm Crodel's report that there exists a definite relationship between the determined contractile force of the uterus and the number of uterine contractions required to complete the first stage of labor. Too many other factors are involved, namely the size of the fetal head, the pelvic measurements, the pelvic inlet, etc. The authors conclude that this method is of no value in prognosticating the progress of labor.

RALPH A. REIS.

Vignes, Landrieu, and Lerouge: Presentation of a Utero-Tensometer, *Bull. Soc. d'obst. et de gynéc.*, p. 396, June 1934.

In order to study the activity of the uterine musculature during labor we may employ either internal or external hystero-graphy. The former has certain inconveniences, such as contractions due to the foreign body and danger of sepsis. External hystero-graphy avoids these disturbances. Vignes, Landrieu and Lerouge used to rely upon clinical judgment for the appreciation of uterine activity but such opinions are not accurate and are subjective. They have, therefore, devised a special dynamometer for studying the action of the uterine musculature by external means. In certain cases of induction of labor by means of a sound and by means of medication they observed a temporary tetany of the uterus followed by regular contractions. In some instances, labor pains failed to follow the tetany. They observed arrest of labor in a case after the use of pituitary extract.

J. P. GREENHILL.

Held, E.: The Number of Contractions in Labor, *Rev. franç. de gynéc. et d'obst.* 29: 673, 1934.

Held believes that a test of labor begins with the rupture of the bag of waters. He believes that every effort should be made to keep the membranes intact until there is complete dilatation of the cervix. This diminishes the risk to both mother and child and favors easy engagement of the fetal head. This procedure is especially to be carried out in cases of dystocia. The author kept a record of the number of uterine contractions in each stage of labor. Lack of progress in dilatation after 100 uterine contractions in certain cases is an indication for interference. Vaginal or abdominal intervention will depend upon engagement or nonengagement of the head, as well as the state of the soft parts and other obstetric factors.

J. P. GREENHILL.

McIlroy, Louise, and Rodway, Helen E.: The Alleviation of Pain in 560 Cases of Spontaneous Labor, *J. Obst. & Gynec., Brit. Emp.* 40: 1175, 1933.

Five hundred and sixty primiparas delivered spontaneously were given sedatives during labor and delivery. During the first stage opiodine or morphine, with or without potassium bromide and chloral hydrate, were given. During the second stage of labor the anesthetic which gave the most favorable results was undoubtedly a mixture of gas and oxygen. During delivery in some cases the mixture was supplemented by chloroform or ether. It was found that a combination of potassium bromide and chloral hydrate in the first stage is a useful and safe sedative, especially in excitable and nervous patients, and it has no apparent effect on uterine contractions. Morphine is the most valuable of all sedatives. It is rare to find any adverse effect upon the mother or the fetus. It is much safer than many of the toxic barbiturates now in use. Its effect is intensified and prolonged by giving it in 50 per cent solution of magnesium sulphate. Observations upon the effect of morphine on the infant showed that spontaneous respiration took place no matter how late the administration of the drug. Nitrous oxide and oxygen gave the best results for administration in the second stage of labor and during delivery. The duration, strength and frequency of the contractions increased in over 50 per cent of the cases. There were not any cases of postpartum hemorrhage due to the administration of drugs.

WILLIAM F. MENGERT.

Rivett, L. C.: Chloroform Capsules During Labor, *Brit. M. J.* 2: 778, 1933.

Rivett finds that gas with oxygen is the nearest approach to the ideal for analgesia in labor pains. However, because of the expense and somewhat cumbersome machinery this is seldom used in England and Wales. Chloroform very closely approaches gas-oxygen as an ideal. About 60 per cent of the labors, about 450,000, are conducted by midwives without the aid of a medical practitioner. In order to overcome the risk of a midwife's applying too much chloroform from a drop bottle, the author had chloroform put up into crushable glass capsules and a mask fitted with a little clip into which these capsules can be inserted one at a time and in over 3,000 cases at Queen Charlotte's Hospital, these capsules were found eminently satisfactory. The capsule wrapped in gauze and placed in the clip is crushed when the pain comes on and the mask applied two inches free of the patient's face. As soon as each pain has ceased the mask is removed and the next pain awaited. These capsules are intended only for analgesia, and not anesthesia. They are meant only for pains at end of the first stage or in the second stage.

F. L. ADAIR AND IRA BROWN.

Le Lorier, and Mayer, M.: Twenty-Six Obstetrical Anesthesias With Evipan Sodium at the Port Royal Maternity, *Bull. Soc. d'obst. et de gynéc.*, p. 342, 1934.

The writers used evipan sodium in 26 obstetric cases. They injected the drug intravenously and consider this drug to be very useful; however, great care must be exercised. Its advantages are as follows: The anesthesia is produced immediately, it is short, the awakening is agreeable, there is no postanesthetic discomfort, and there are no untoward effects on the uterine contractions nor on the child. The dangers are reduced if one chooses only young women who are not fatigued, or ill, and who do not have hypertension, if the injection is given slowly and if the patient's reactions and reflexes are scrupulously watched.

J. P. GREENHILL.

Irving, Frederick C., Berman, Saul, and Nelson, Bristol, H.: *The Barbiturates and Other Hypnotics in Labor*, Surg. Gynec. Obst. 58: 1, 1934.

At the Boston Lying-In Hospital for one year an investigation was made into the amnesic, analgesic, and anesthetic properties in labor of drugs in more or less common use. Eight types of anesthesia were used, and 860 patients were studied.

*Pantopon and scopolamine* in combination proved not to be satisfactory hypnotics, since only 34 per cent of patients had no memory of their labor and only 33 per cent of the infants breathed immediately after birth. There was also a prolongation of labor in primiparas, the operative incidence was high, and the incidence of large blood loss was the highest encountered in the study, being 25 per cent.

With *pantopon and rectal ether* there occurred only 18 per cent of complete amnesia, the lowest in the series. Sixteen per cent of the patients lost over 300 c.c. of blood, the second highest in the study. There was, however, a low incidence of excitement.

*Pernocton* is evanescent in its action and cannot be given until the end of the first stage of labor. It produces a low incidence of amnesia and considerable excitement.

*Sodium amytal and scopolamine* resulted in complete amnesia in 80 per cent of cases. No marked effect in delaying the initial respiration of the infants was noticed. There was, however, a fairly high incidence of restlessness and the return to consciousness was prolonged.

*Pentobarbital and scopolamine* produced 86 per cent of complete amnesia, the highest in the study and the greatest percentage of infants, 63, breathed immediately after birth. The operative incidence was low. The recovery after delivery was not lengthened. The frequency of excitement, however, was considerable, being 16.20 per cent. This is the only valid objection to the method.

With *sodium amytal and rectal ether* there was little restlessness, but the percentage of complete amnesia was only 72 per cent.

*Pentobarbital and rectal ether* were even less effective in producing amnesia, although the absence of excitement was similar.

*Pentobarbital and paraldehyde* produced a moderate incidence of complete amnesia. Twenty-four per cent of the patients, however, were sufficiently excited to require restraint.

In no case in any group was there noted an untoward effect upon mother or child.

Pulse, respiration, or systolic blood pressure showed no characteristic variations during or immediately following labor in any group.

WM. C. HENSKE.

Minamikawa, K.: *Manual Dilatation of the Cervical Canal*, Japanese J. Obst. & Gynec. 16: 163, 1933.

In the opinion of the author a cervix can be completely dilated manually. His average length of time for this procedure was seven minutes, but it never required more than twenty minutes. He considers eclampsia and abruptio placentae as absolute indications for this procedure, but he also believes the operation should be used in cases of placenta previa, transverse presentation, cardiac and renal diseases. He mentions that the cases in which the cervix is dilated less than three fingerbreadths at the beginning of the procedure are fraught with some danger but those with more than this amount of dilatation give no concern. The amount of cervical damage varies inversely with the duration of



pregnancy. There is no risk of infection if the operator is clean. No instruments are used, only the operator's fingers and since these tire readily they cannot do any great damage to the cervix. After complete dilatation is brought about, delivery is accomplished by version and extraction, hence there must be no pelvic contraction when cases are chosen for manual dilatation of the cervix.

J. P. GREENHILL.

**Beruti, Leon, and Diradourian:** Early Artificial Rupture of the Bag of Water and Antispasmodics in Functional Anomalies of the First Stage of Labor, *Semana méd.* 2: 361, 1933.

From a careful study of 31 primiparas and 31 multiparas the authors conclude: In cases of primary or secondary dynamic insufficiency artificial rupture of the membranes, in general, intensifies the contractions. In cases of inertia the combination of small doses of pituitary extract with an antispasmodic gives good results. In the presence of spastic conditions rupture of the membranes is indicated, when their persistence is the cause of the inertia and prolongation of the labor. When it is impossible to determine the cause of the functional abnormality antispasmodics should be administered. If, after the antispasmodics have regulated the contractions, they should cease, the membranes should be ruptured and an antispasmodic with small doses of pituitrin be given. Following such treatment the cervix dilates rapidly and the period of expulsion is short.

The best results were obtained in those patients in whom the cervix was dilated more than 4 cm., and especially when the presenting part was high without any disproportion.

The administration of large doses of antispasmodics predisposes to a greater amount of bleeding during the third stage. The rupture of the membranes before complete dilatation does not delay puerperal involution.

The antispasmodics used were: (1) A combination of pantopon, papaverine and spasmalgine; (2) papaverine and atropine sulphate, and (3) suppositories containing belladonna and scopolamine.

JAMES M. PIERCE.

**Voron, J., and Pegeaud, H.:** The Treatment of Contracted Pelvis at the Lyon Obstetric Clinic During 1931 and 1932, *Rev. franç. de gynéc. et obst.* 29: 481, 1934.

The 221 cases of contracted pelvis observed were treated in a variety of ways. The greatest number, 108, were delivered through the vagina after a test of labor. In this group were one maternal and 4 fetal deaths. In 21 other cases the test of labor had to be terminated by hysterotomy. In this series one mother and two babies died. In 66 cases the authors induced labor before or near term and all of these women delivered spontaneously. In this group there were no maternal or fetal deaths. In 21 cases where labor was induced, operative interference had to be employed and while no mothers died, two babies perished. Five prophylactic cesarean sections were performed with one maternal death. Hence in the entire series of 221 cases there were three maternal and eight fetal deaths.

J. P. GREENHILL.

**Hanson, Samuel:** The Narrow Bispinous Diameter and the Persistent Occipito-posterior Position, *Surg. Gynec. Obst.* 59: 102, 1934.

The object of this study is to determine what influence, if any, the narrow bispinous diameter may exert on the mechanism of labor, particularly so far

as the incidence of the persistent posterior position is concerned. Observations were made on a series of 2,254 consecutive cases; 811 of these were primiparas. The bispinous diameter was measured in all cases. Pelves with a bispinous diameter of 9.5 cm. or less were classed as narrow. According to this classification in 143 primiparas in whom the bispinous diameter was found to be narrow, there were 27 cases (18.9 per cent) of persistent occipitoposterior position. This incidence is approximately thirteen times greater than the incidence of the persistent posterior position in pelves with a normal bispinous diameter. The persistence of a posterior position may, therefore, be anticipated early in labor if the bispinous diameter is narrow and operative intervention may be instituted under the most favorable circumstances.

WM. C. HENSKE.

Wodon, J., and de Guchteneere: Retention of Membranes After Labor, *Rev. franç. de gynéc. et d'obst.* 29: 489, 1934.

The retention of part of the fetal membranes after delivery of the child does not warrant intrauterine intervention because it does not cause hemorrhage or serious complications. In 60 per cent of such cases there is no morbidity, in 30 per cent the temperature is only slightly elevated and in but a small proportion of cases is the fever high. The incidence of high fever in these cases is no greater than in the cases where the membranes are entirely expelled. In cases where all the membranes are retained and high fever appears early, it is permissible but not indispensable to perform a curettement. However, this intervention is only of advantage if it is performed before the fifth day.

J. P. GREENHILL.

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Roxas, Baens, and Katigbak: Rupture of the Uterus. Report of Cases in the Philippine General Hospital from 1910 to November, 1933, *J. Philippine Islands M. A.* 14: 37, 1934.

The incidence of institutional ruptures in the charity ward of the Philippine General Hospital is 1 to 1,565, comparing favorably with the incidence in the New York Lying-In Hospital, 1 to 810. Our percentage of mortality in uterine rupture is 100 fetal and 85.7 maternal. Asa Davis from the New York Lying-In Hospital, gives 69.44 per cent maternal mortality in complete rupture and 12.5 per cent in incomplete rupture. Koblanek gives 73 per cent to 78 per cent. Our maternal mortality from 1928 up to the present time is 78.1 per cent.

The mortality percentage could be decreased only by a campaign of instruction among the masses, the elimination of the old midwives, and also by better training of physicians in obstetrics and gynecology. Legislation governing obstetric practice should be passed along the lines of the law passed recently by the legislature, prohibiting midwives from administering pituitrin during labor and from performing internal examination.

C. O. MALAND.

## Correspondence

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### Effect of Large Doses of Estrin on the Human Menstrual Cycle

*To the Editor:*

Since estrogenic hormones play a vital rôle in the physiology of menstruation, it is important to determine whether the administration of large amounts of such substances can produce any disturbance of the cycle. An opportunity to study this question occurred while observing a series of 12 patients treated with amniotin for pelvic inflammatory disease.

The preparation was specially made up in oil by Messrs. E. R. Squibb and Sons, through the courtesy of Doctor J. F. Anderson and Doctor J. A. Morrell. Each cubic centimeter contained 500 or 1,000 rat units. The patients were given one daily intramuscular injection over periods of from eight to twelve days and received total dosages varying from 3,000 to 9,500 rat units. The amniotin was administered at all phases of the menstrual cycle.

It was found that in 8 out of the 12 cases there was no change as regards the duration of the cycle, the length of the periods, or the amount of blood loss. In 2 instances there were irregular uterine hemorrhages, and in 2 others the period following the administration of amniotin was noted as being more profuse. Since one-third of the women with pelvic inflammatory disease have abnormal uterine bleeding (*Fluhmann, C. F.: J. A. M. A. 97: 694, 1931*), the finding in these 4 patients may very well be attributed to this condition and not to the hormone administered.

It would seem, therefore, that the administration of as much as 9,500 rat units of estrin during the course of a normal menstrual cycle does not produce any disturbance in that cycle nor in the succeeding menstrual period.

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY,  
STANFORD UNIVERSITY SCHOOL OF MEDICINE,  
SAN FRANCISCO, CALIFORNIA.

C. F. FLUHMAN, M.D.  
P. E. HOFFMANN, M.D.

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## Item

### American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants for certification will be held in various cities of the United States and Canada on Saturday, March 24, 1935. Case histories for review may be filed with the Secretary any time prior to this date after the approval of a candidate's credentials.

The general examination for all candidates will be held in the Atlantic City General Hospital on Monday, June 10 and Tuesday, June 11, 1935, immediately prior to the scientific session of the American Medical Association.

An unusual number of candidates is expected for this meeting, and on this account early application is advisable in order to qualify. Applications for Group B candidates must be received not later than February 23, 1935, and for Group A candidates not later than May 10, 1935.

For further information, booklets, and application blanks apply to the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, (6) Pa.

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## Original Communications

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### INTESTINAL COMPLICATIONS RESULTING FROM PRO- LONGED RADIUM AND X-RAY IRRADIATION FOR MALIGNANT CONDITIONS OF THE PELVIC ORGANS\*

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*(From the Cleveland Clinic)*

LAST year, before this Society,<sup>1</sup> Dr. Palmer Findley presented a paper on the complications of radium therapy for carcinoma of the cervix, and it is not my intention at this time to repeat those varied adventitious circumstances which he covered so well, but merely to call your attention to the possibility of intestinal injury by radiation therapy and the importance of its recognition.

The present study directs attention to a rather new clinical entity<sup>2</sup> which may develop and call for surgical intervention many months or years after complete regression or cure of the cervical cancer. In a series of 520 patients with cervical carcinomas, who received irradiation therapy at the Cleveland Clinic, there have been seven known cases of benign stricture of the intestine causing obstruction which might easily have been construed as, or confused with, metastatic deposits. In five of these cases the obstruction was in a movable segment of the sigmoid and in two cases in the small intestine. All these strictures were observed in patients who had been irradiated for carcinoma of the cervix, but the increasing use of radiation for other conditions which necessitate exposure of the intestines may result in similar complications. Subsequent to the irradiation therapy no evidence of

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carcinoma was found in these cases, and judging by present-day standards, none of these patients received excessive irradiation. Since similar methods of therapy are in general use, it seems probable that the incidence of the lesion is greater than is surmised at the present time; and if similar cases have been attributed to metastasis in the past, the mortality statistics relating to metastasis from cervical carcinoma are open to question. Desjardins<sup>3</sup> in an exhaustive report has called attention to intestinal injury produced experimentally by irradiation.

There are many reports dealing with the manifestations of acute injury of the intestine following irradiation, both experimental and clinical, but I have not been able to trace any reports on patients who have recovered from the acute symptoms and have later developed the chronic condition herein described. If such cases have been described this report adds seven cases of intestinal obstruction which developed in patients eight months to eight years after radiation therapy for cervical carcinoma.

The rate of recurrence of cancer is so high that almost any abdominal or pelvic pain may quite naturally and logically be attributed to malignant extension or metastasis. If the condition actually is a benign stricture caused by irradiation, it is quite obvious that additional x-ray treatment would only aggravate the condition and hasten the end. Therefore, one should always keep in mind the possibility that a patient who exhibits unusual abdominal symptoms, particularly if they simulate intestinal obstruction, several months or even years following radiation therapy, may have a stricture of the intestine and may be restored to normal health by resection of the lesion. Before attributing this disability to metastasis, thorough re-examination by sigmoidoscopic and roentgenographic studies should be made to eliminate the possibility of this curable complication. While roentgen ray examinations demonstrate lesions in the sigmoid quite readily, strictures in the small intestine are quite difficult to visualize unless the obstruction is practically complete. In this type of case it is inadvisable to give barium in any large amounts, and therefore exploratory operation is warranted; especially in patients in whom there is no evidence of recurring carcinoma in the pelvis.

#### CASE REPORTS

CASE 1.—A woman, aged sixty years, when first examined had a carcinoma of the cervix uteri, extending into the broad ligament. Biopsy made at the time of treatment showed a squamous cell carcinoma, and the patient was treated by irradiation with radium and roentgen rays.\*

\*One tube containing 170 mc. radon was inserted into the cavity of the uterus and cervical canal for twelve hours, producing a total irradiation of 2,040 mc. hours. Three days later, roentgen therapy was started. Two months later a second radium treatment was administered to the cervix, using 220 mc. of radon in four tubes against the cervix for ten hours, totaling 2,200 mc. hours, or a total of approximately 4,240 mc. hours for the two radium treatments. The actual amount of radiation received represents about 3 per cent less than these figures when calculated according to the time the radon is in place.

Follow-up examinations had shown no evidence of malignant disease, and the patient had been in excellent health for over two years after the last radium treatment. Then she began to have unusual constipation, which became progressively more severe and at the time of readmission, a few weeks after its onset, she had symptoms and signs of intestinal obstruction. Proctoscopic examination yielded no information and neither blood nor mucus was seen in the bowel. Roentgen examination of the colon revealed an obstructing lesion in the sigmoid colon, which was believed to be due to carcinoma. At operation, the lesion had the characteristics of a benign stricture. There were bands of adhesions encircling the sigmoid colon at the site of the lesion, and these were attached to the fundus of the uterus. The adhesions were severed, this portion of the colon was resected, and an end-to-end anastomosis was made. The pathologic diagnosis was chronic inflammation. The patient made a good recovery from the operation, and has reported normal health on numerous occasions during the two and one-half years since the resection was performed.

CASE 2.—The patient, aged fifty-two years, had had a pelvic abscess years previously, and came to the Clinic because of pelvic pain. The cervix uteri was firm, enlarged, and nodular, especially on the right side, and bled easily. There was no thickening of the broad ligaments. Squamous cell carcinoma was revealed by biopsy and radium and roentgen therapy was administered.\*

For a year and a half after the irradiation, follow-up examinations had shown no evidence of disease, and the patient had been in excellent health. Then she began to have severe pains in the bladder, associated with some blood in the urine. These symptoms persisted for three weeks. When the patient returned to the Clinic, cystoscopic examination revealed several submucous hemorrhages on the posterior wall of the bladder, in the center of which was a white, irregular area about 2.5 cm. in diameter. Subsequent examinations showed a definite ulcer in the irregular area mentioned. One year following the initial cystoscopic examination, the ulcer had disappeared completely, except for a small area of submucous hemorrhage due to separation of the slough a few days previously.

Approximately a year and nine months subsequent to treatment the patient began to have unusual abdominal symptoms, simulating intestinal obstruction. Roentgen examination of the colon showed no obstruction at the time of the onset of these symptoms. No further roentgen studies were made. The initial attack soon subsided, but two months later there was a recurrent attack which was more severe, and operation was performed. There was an old inflammatory process in the uterine tubes, but no evidence of carcinoma could be found. About 25 cm. proximal to the rectum there was a definite, almost complete obstruction of the sigmoid colon. It was not adherent to the pelvis. It seemed as if there were a cicatricial band in the bowel wall, with very little inflammatory reaction outside. Resection was considered, but it was deemed more advisable to make an anastomosis around the obstruction, particularly in view of the fact that the sigmoid colon was unusually long. A side-to-side anastomosis was made. The last follow-up letter from the patient, five years after operation, states that she is in normal health.

CASE 3.—The patient, aged forty-one years, had an enlarged cervix uteri which was bleeding and ulcerated. The principal involvement was inside the cervix, extending into the uterus and outward through the cervix, lateral to the external os. The biopsy showed squamous cell carcinoma. Radium and roentgen therapy was administered.†

\*Two tubes containing 305 mc. of radon were inserted into the uterus and cervix and two tubes containing 140 mc. of radon were placed against the cervix for six and a half hours producing a total irradiation of about 2,750 mc. hours. Twelve days later roentgen therapy was started.

†One tube containing 106 mc. of radon was placed in the fundus of the uterus, one tube containing 247 mc. of radon was placed in the cervix, and four tubes containing 142 mc. were placed against the cervix for eight hours, or a total of approximately 3,960 mc. hours. One month later roentgen therapy was administered.

The frequent transitory rectal sequelae immediately following these treatments were prolonged in this case. For six months, the patient complained of loose stools containing unusual quantities of mucus. It is significant to note here that there was no lesion in the rectum opposite the treated area where one would presume the maximum effect of radium would prevail. The following months there was marked constipation, and after a period of eleven days without a stool, the patient suffered from considerable abdominal distention, and was readmitted to the hospital with a diagnosis of intestinal obstruction. Follow-up examinations had shown no evidence of recurrence of the malignant growth in the cervix or adnexa. Proctoscopic examinations had shown no evidence of disease. Laparotomy was not performed at this time, since her symptoms were relieved by the use of enemas and hot fomentations over the abdomen.

She was readmitted to the hospital at two- and six-month intervals subsequently. An attempted barium enema was expelled as soon as it had reached the sigmoid colon, apparently indicating obstruction at this level.

Fifteen months after irradiation a cecostomy was done and a large tube was inserted for irrigations. Later, a colon roentgen examination, during which the barium suspension was injected through the colostomy tube, revealed a definite obstructing lesion in the sigmoid colon. At the subsequent operation, performed recently, the lesion proved to be a benign stricture causing complete obstruction. This portion of the colon was resected, and an end-to-end anastomosis was made. The patient's recovery following operation was uneventful and the cecostomy closed itself.

CASE 4.—The patient, fifty years of age, had a diffuse carcinoma of the cervix uteri, involving chiefly the cervical canal (Stage 1). Squamous cell carcinoma was revealed by biopsy and the patient was treated by irradiation.\*

Subsequent examinations revealed satisfactory progress, and the patient was in good health except for an attack of gallstone colic. Approximately three years following irradiation, she stated (for the first time) that she had had some blood in the stools off and on during the previous year, which she attributed to hemorrhoids. Unusual constipation was also present. Pelvic and proctoscopic examinations showed nothing except the hemorrhoids, and those were treated by the injection method. A colon roentgen examination, however, revealed an annular filling defect in the sigmoid colon, and reexamination one month later revealed the same finding. Bleeding continued at intervals and in one instance a cupful of blood clots was passed.

At operation (three and one-half years following irradiation) the lesion proved to be a benign stricture. This portion of the colon was resected and an end-to-end anastomosis was made. Death from local peritonitis followed, fifteen days after the operation.

CASE 5.—The patient, aged fifty-nine years, suffered from a rather extensive carcinoma of the cervix uteri, involving chiefly the anterior lip of the cervix and extending into the vaginal wall. The lesion, as determined by biopsy was a squamous cell carcinoma. The patient was treated by radium irradiation,† but received no roentgen therapy.

\*Two tubes containing 244 mc. of radon were inserted, one in the cervix and one against the cervix, for ten hours, or a total of approximately 2,440 mc. hours. One month later, roentgen therapy was administered.

†The tube containing 266 mc. of radon was inserted into the cervical canal and ten radium needles, each containing 10 mg. of radium were inserted into the carcinomatous mass, approximately 1 centimeter apart; and one tube containing 107 mc. of radon was placed against the anterior lip of the cervix, a total of 373 mc. of radon and 100 mg. of radium for 7½ hours, equivalent to about 3,729 mc. hours.

The patient made satisfactory progress but complained of slight constipation which was unusual for her. Seven months following radium irradiation she stated that during the past few weeks the constipation had become more severe and that she had passed darkened blood, blood clots, and mucus by rectum, associated with cramplike abdominal pains. Pelvic examination showed nothing of significance, but roentgen examination of the colon revealed a conical, fixed, concentric narrowing in the midsigmoid area, believed to be due to an irradiation stricture. At operation the stricture was immediately behind the fundus of the uterus. This area appeared to be anemic as compared with the remainder of the sigmoid colon. A cecostomy was performed and one month later a resection of the lesion, and an end-to-end anastomosis. The patient was discharged from the hospital one month after operation, at which time the stools were normal.

CASE 6.—The patient, aged fifty-eight years, had a carcinoma of the cervix uteri, involving chiefly the posterior lip and the posterior vaginal wall. The pathologic diagnosis was squamous cell carcinoma. Radium therapy was followed by roentgen irradiation.\*

For five months the patient showed satisfactory progress with complete regression of the lesion, but did not return for the usual subsequent examinations. Two months later, in a letter from the patient's husband who was a physician in a distant town, it was learned that the patient had been confined to bed for a month because of abdominal pain, nausea, and pronounced vomiting. He stated that examination revealed no evidence of carcinoma in the cervix or in the neighboring structures. Death followed one month later. Autopsy was performed which revealed an inflammatory stricture of the small intestine, causing a definite obstruction. The exact relation of this area to the uterus was not stated, but examination of this area of the intestine and the uterus, after removal from the abdomen, revealed adhesions on the peritoneal surfaces of both.

From these findings it may be inferred that the stricture of the small intestine involved an area adjoining the uterus, that fibrous adhesions formed between the two, and that the cause of death (since no other cause was considered or found) was severe toxemia, resulting from obstruction of the small intestine.

CASE 7.—The patient, aged forty-two years, was admitted to the Clinic on the first of June, 1926, with a history of vaginal bleeding for one year. Examination showed extensive papillary carcinoma of the cervix with involvement of the vaginal wall anteriorly and posteriorly, but apparently there was no invasion of the broad ligament. Radium and roentgen irradiation were administered in June, 1926.†

About six months later the patient reported that for a month she had been having trouble with her rectum. The symptoms included tenesmus, mucus, and blood in the stools; this gradually subsided and when the patient was examined a year after treatment there was a narrowing of the rectum opposite the cervix, but the opening easily admitted the index finger. The patient had no abdominal complaints.

In October, 1930, more than four years after irradiation, the patient complained of recurring attacks of abdominal pain which her doctor attributed to gallbladder disease. Roentgenographic examination of the gastrointestinal tract at that time showed no abnormality except a nonfunctioning gallbladder. The attacks of pain continued at occasional intervals until March, 1934, when she suffered a very severe

\*One tube containing 118 mc. of radon was placed in the cervix and another tube containing 177 mc. of radon was placed against the posterior lip of the cervix, for ten hours, or a total of approximately 2,956 mc. hours. One and a half months later roentgen therapy was administered.

†The first application of radium consisted of 3,381 mc. hours with tubes and needles in and against the cervix, and roentgen irradiation was given about three weeks later. A second application of radium to the cervix, amounting to 1,369 mc. hours was administered about a month after the roentgen therapy.



attack, was ill with abdominal pain, nausea, and vomiting for two weeks and lost a great deal of weight. She reentered the Clinic Hospital on April 7, 1934, nearly eight years after the course of radiation therapy. While at the time of hospitalization, there was no evidence of obstruction it was felt that the last attack simulated an obstruction and operation was advised.

Exploratory laparotomy was performed on April 10, 1934. In the small intestine, 3 feet from the ileocecal valve there was an almost complete obstruction with collapse below and considerable dilatation above the stricture. About 4 inches above this there was a slight narrowing of the lumen. A resection of about eight inches of small intestine and an end-to-end anastomosis was made. The patient made an uneventful recovery and was out of the hospital on the fourteenth day. On the fifteenth postoperative day she experienced a sudden severe pain in the right lower quadrant and some abdominal distention, but there was no elevation in temperature or increased pulse rate. The patient was treated expectantly for five days apparently satisfactorily, when distention recurred and exploration was done. There was some free fluid in the abdomen and some distended coils of intestine one of which was used for ileostomy. This functioned quite satisfactorily but the patient gradually failed and died, about two weeks later, on May 13, 1934.

*Pathologic Report.*—Microscopic: A longitudinal section of the small intestine showed marked thickening and dense fibrosis of the serosal coat, in which there were large numbers of greatly thickened arteries, showing varying degrees of obliterative endarteritis, degeneration of the lamina elastica, and hyalinization of the intima, with no calcification present. In some areas, there was localized, perivascular, inflammatory infiltration, with plasma cells predominating. There was considerable, diffuse increase of fibrous tissue in the muscular coat, and fibrosis of the submucosa. The mucosa was somewhat atrophic, contained very little lymphoid tissue and showed mild, diffuse, inflammatory infiltration, with numerous eosinophiles and plasma cells present. In one area, there was active ulceration, with almost complete destruction of mucosa. The base of the ulcer extended into the muscular coat. There was some fibrinous exudate and many leucocytes, together with plasma cells, eosinophiles, and lymphocytes in the exudate. Ganglion cells of the submucosa showed extensive degenerative changes in the neighborhood of the ulcer. There was no evidence of neoplasm.

#### DISCUSSION

This group of cases is of particular interest to me because I administered the radium in all cases and have had the surgical management of the resulting complications. The x-ray therapy was administered by Dr. Portmann. Obviously, as is the case in any pathologic process the factor of particular interest is the causation and possible prevention of the lesion. In this case the radium therapist is likely to blame the x-ray therapist and vice versa, whereas both probably have contributed to the causation of the lesion. It is significant to note that in this series only one patient had any lesion in the rectum opposite the cervix where the maximum intensity of radiation would be delivered. In Case 7 with the obstruction of the small intestine there was a slight narrowing of the rectum which was readily dilatable. This would seem to justify the statement that the radium dosage used in this series was not excessive.

That roentgen irradiation is not entirely responsible is a justifiable assumption, since one patient (Case 5) received no x-ray therapy. Furthermore the lesion in this case was not at the point of maximum intensity but in the sigmoid several inches away. One then must search for causes which contribute to fixation of a certain loop of small or large intestine in the pelvis which is the recipient of the maximum radium and roentgen dosage at that particular point. Previous inflammatory disease of the pelvic organs, either specific or post-partum, might tend to fix a loop at a vulnerable point, yet this was not a factor in this group of cases because in only one was the bowel fixed in the bottom of the pelvis by an apparent previous inflammatory process.

From my observations I would venture the following explanation which may apply in the majority of cases: The initial insult is delivered by radium. If a loop of small or large intestine remains in the same position in the culdesac during the entire time of radium irradiation, the erythema produced at this point may be sufficient to produce a simple local peritonitis which would fix the bowel at this point temporarily. Before the exudate is completely absorbed, roentgen rays are administered, thus furnishing additional irritation which is sufficient to cause an ulceration in the mucosa, and eventually goes on to stricture formation. As time passes the exudate is absorbed and the bowel becomes free, which is the general finding at operation.

Whether this intestinal lesion be due to one agent or the other or a combination of both, it behooves us to devise ways and means to prevent it. Change of position of the patient during treatment suggests itself as an aid, but this would not be entirely safe because of the danger of dislodging the radium tubes and possibly causing damage to the rectum or bladder. However, a Trendelenberg position maintained during treatment may help to keep the intestines out of the pelvis while the latter is being irradiated both by radium and x-rays. If the theory of some fixation of a loop of intestine is tenable, drugs to stimulate peristalsis may be considered, and it might be advisable to give  $\frac{1}{2}$  to 1 c.c. of pitressin every four hours while the radium is in place or just previous to an x-ray treatment, in order to keep the intestines moving, and thus, to preclude excessive irradiation of any one loop.

In presenting these intestinal complications I do not wish to convey the idea that I disparage the present-day treatment of cancer of the cervix. I believe it is the best we have to offer and I shall continue to use it. However, on the basis of the experience here reported, I would interject a word of caution regarding the step that is being taken at the present time, the stepping up of the voltage many times more than has been customary, because I think increased voltages carry a definite potential danger of damage to the intestines.

## CONCLUSIONS

The recognition of the possibility of benign stricture of the intestine as a complication following radiation therapy often months or years later, is of utmost importance, for it can very easily be confused with recurrence of malignancy. Its detection and surgical treatment may salvage the lives of many patients otherwise regarded as having hopeless malignancy.

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## A CRITICAL STUDY OF FIVE HUNDRED CASES OF ECLAMPTOGENIC TOXEMIA\*

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THESE data have been compiled from an analysis of five hundred consecutive cases of eclamptogenic toxemia occurring in my clinics at the University of Illinois and the University of Iowa in the last ✓ twelve years approximately.

The reason for this presentation is to bring before you the results of a simple management, adaptable to any clinic or hospital or the private practice of any well-trained physician. It is also hoped that it may throw some light on some of the moot questions in eclampsia, such as the danger of operative interference, whether or not cesarean ✓ section is justifiable, whether or not the phenolsulphonephthalein test is of prognostic value.

The series is relatively small, but it has the advantage of having been slowly accumulated under one system of treatment which has not been deviated from appreciably from year to year. The management of practically the entire series of patients has been under my personal supervision. Almost all of the cesarean sections have been done by me. Forceps deliveries, versions, and bag inductions of labor have been done by me or my residents.

That part of the clinical material gathered in the University of Iowa was composed for the most part of young, illegitimately pregnant

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girls who were sent in from the surrounding country about the twenty-eighth week to stay in our prenatal home until confinement. They were under the close supervision of a nurse housekeeper who followed instructions as to their diet and exercise. They were seen twice a week routinely by students and interne; the blood pressure readings were taken and the urine specimens were examined. All patients showing even moderate grades of toxemia were sent into the hospital.

The Illinois group were all charity cases from the slums of Chicago. Most of them were ignorant women, many difficult to instruct because of their limited knowledge of English. They were seen routinely in our prenatal clinic by my associates who sent into the hospital all patients showing evidences of toxemia which did not yield readily to home management in a few days.

All cases were ward patients, none had private nursing care or any special attention beyond what would be ordinarily given a sick patient in an obstetric ward. It is obvious, therefore, that no specially favorable factors entered into the care of these patients to account for our results. Those patients who delivered spontaneously or by breech extraction were delivered by the internes or resident physician, in most cases without the presence of a member of the teaching staff.

As I have stated before, our conception of eclamptogenic toxemia is a metabolic disturbance due to overproduction of protein split products, or to decreased detoxification of the same, or both. These toxins circulating in the blood act first and most powerfully on the highly specialized cells of the body, especially those which have to do with their detoxification and excretion, the liver and kidney. Damage to these organs completes the vicious circle and the level of the toxins in the blood rises unless the production of the toxins is curtailed or the reserve power of the kidney and liver are sufficient to overcome the difficulty by elimination of the toxins or by neutralizing them.

This view has much in it comparable to that expressed by Solomons before this body two years ago, although he feels that reduction in proteolytic ferment content of the blood may be an important factor. Our work on the Abderhalden test in 1914 seemed to show the ferment content of the blood increased in eclamptogenic toxemia.

The brain, the heart muscle, and the retina are also secondarily affected by the intoxication which results in decrease in their functional efficiency.

We believe nephritic toxemia to be an eclamptogenic toxemia fostered by the inability of the kidney to eliminate at the usual rate the normal amount of toxins produced by a normal pregnant woman.

We feel that it is a mistake to confuse the issue by splitting up the cases of eclamptogenic toxemia into low reserve kidney (Stander),

eclampsism, preeclampsia, and eclampsia. It would be equally logical to divide lobar pneumonia into one lobe pneumonia or two lobe pneumonia, or to speak of one kind of typhoid fever with perforation or hemorrhage and another kind without. If a patient has chronic nephritis and develops diabetes, it may alter the course and symptoms of the diabetes, but the fundamental cause and effect of the diabetes remain the same.

Hofbauer has a very similar conception of the etiologic factors concerned in the disease. He stresses the importance of the posterior pituitary hormone as a contributing factor, producing angiospasm which results in tissue anoxemia, especially in liver, kidney, heart muscle, and brain.

The sources of the toxins are three in number: (1) The fetus and placenta, (2) the exogenous protein metabolic products, and (3) the products of endogenous protein metabolism.

The control of these sources of intoxication is only partially possible. In our opinion little if anything can be done to regulate the toxins produced by the fetus and placenta. Our conception of these structures is that biologically they are comparable to a malignant tumor and can be about as easily influenced by ordinary measures.

The exogenous protein metabolism can be controlled by the nature and amount of food intake. The endogenous protein metabolism can be reduced significantly by restricting bodily activity, thus reducing the protein split products from this source.

The level of toxins in the blood from all of these sources can be minimized by stimulating bowel activity with magnesium sulphate, by promoting diuresis, and by venesection.

#### PROCEDURE

The patients as they enter our clinic are immediately put at bed rest and given nothing but milk by mouth. They may have a quart or more a day. An ounce of magnesium sulphate is given night and morning until watery stools are obtained, after which it is given only in the morning. A phenolsulphonephthalein test is run according to the original Gerrhety and Roundtree technic of intramuscular injection. I find that nearly every interne has his own ideas as to how the test should be performed, and only by insisting can one expect to have it done properly and thus have the results comparable with other cases.

A catheterized specimen of urine is examined. A blood pressure reading is taken and recorded night and morning, in all cases where it is above 140 mm. When the pressure drops and the albumin disappears, fruits and vegetables are added to the diet, and the patient is permitted room exercises. If the symptoms do not reappear and the patient is not at term, she is sent back to the out-patient service for bi-weekly prenatal observation.

If she does not respond thus favorably, labor is induced by quinine and castor oil, or if this fails, bag induction is used. In some cases, especially in elderly primiparas, it has been our practice to resort to cesarean section under these circumstances because of the uncertainty of our induction methods, and since we favor taking a slight additional maternal risk for the sake of the baby in these patients.

With a rapidly advancing toxemia there may not be time to try out the conservative management. In these cases we start the eliminative treatment as usual, and at the same time start the induction of labor. Bag induction is used in most cases. If there is a significant pelvic contraction, an organic heart lesion, or other conditions which might become a serious complicating factor in attempting to deliver from below, we do a cesarean section.

In the fulminating cases which go on to convulsions within a few hours after the premonitory symptoms, we do a cesarean section immediately.

Patients admitted in labor showing severe symptoms or in convulsions are treated palliatively with morphine and chloral hydrate per rectum until complete dilatation of the cervix results. If the second stage lasts more than half an hour, labor is terminated by forceps or version, depending upon whether the head is or is not engaged.

Postdelivery, all except the patients with very mild eclamptogenic toxemias are treated as if we expected them to develop convulsions. They are kept on a milk diet until the albuminuria decreases, and the blood pressure declines. It is difficult to convince the internes and resident physicians that all danger is not past as soon as the baby is born. Continued management, however, prevents postpartum convulsions in most cases, or if they occur, it lessens their severity.

#### CLINICAL OBSERVATIONS

The patients were found to be young for the most part. Twenty per cent were less than twenty years of age, about 50 per cent were between twenty and thirty, and 28 per cent between thirty and forty. This agrees well with the fact that 54 per cent occurred in primiparas, 12 per cent in para ii, 11 per cent in para iii, 3 per cent in para iv, and 12 per cent in para v or over.

These figures compare with those of practically all writers on eclampsia and require an explanation. No very satisfactory explanation of this point appears in the literature. It is difficult to see why women when young and vigorous before they have had a chance to develop serious degenerative lesions in the kidney, liver, heart, and brain should be less resistant to any toxic state than older women. Paramore believes that increase in intraabdominal pressure in these women is the important feature. Alvarez thinks that increased intraabdominal pressure leads to increased permeability of the bowel wall to incompletely broken-down end-products of digestion caused by vascular stasis in the bowel.

The explanation lies, we believe, in the fact that the pregnant state fundamentally requires a marked change in the activities of the glands of internal secretion. The changes are reflected in marked alterations in metabolism. For the primipara undergoing this experience for the first time, the fluctuations may be more marked and the compensatory mechanism less well adjusted than in the woman who has undergone the experience several times. As a result an apparent immunity is developed in the multipara which, however, should not be confused with immunologic reaction in the ordinary sense.

Headache, severe enough to be noted as an important complaint, was noted in 272 of these women.

Pitting edema was found in 325 patients and all cases were excluded from consideration which seem to be on other than a toxic basis. We could not confirm the observation of Williams that lack of edema in eclamptic patients seems to be associated with the more toxic cases.

Visual disturbances were noted in 126 patients. They varied from a slight blurring to inability to count fingers at a few feet distance. None of the patients

showed complete blindness even for a short time. This frequent functional impairment was in marked contrast to the paucity of cases showing changes in the eyegrounds.

Epigastric pain was complained of in 156 cases and was associated with vomiting in 205 cases. These symptoms we feel are due to the irritation of the abdominal and pelvic sympathetic ganglia by the toxins.

Twenty-nine of the five hundred patients developed convulsions in spite of our management. Of these only 13 developed convulsions antepartum. We feel that our conservative management in most cases, and our prompt intervention in those cases not yielding to conservative management, resulted in reducing the number of patients having convulsions, as well as the number and severity of convulsions in each case.

Sedatives were not given to control convulsions in any patient until after the uterus was emptied, even the usual preoperative  $\frac{1}{4}$  gr. of morphine sulphate was omitted in patients requiring cesarean section. On the other hand, morphine and other sedatives were used freely following delivery in all patients in whom convulsions had occurred and in many patients in whom it seemed probable that convulsions were imminent.

Magnesium sulphate injections were used in doses of 20 c.c. of a 10 per cent solution in a few of the milder cases where the patients had convulsions.

Since magnesium sulphate was withheld purposely in all but a few of the cases, it is evident that it is not essential to the management. Treatment by glucose injections as recommended by Titus was withheld for the same reason.

Albuminuria occurred in 265 cases in amounts more than a trace. Red blood cells appeared in 132 cases, hyaline casts were found in 122 cases, and granular casts were present 137 times. These findings stress the fact that the kidney is very little damaged in nearly half of the cases. Some of the 265 patients may have presented albuminuria before they become pregnant.

A phenolsulphonaphthalein test was done on 153 patients. The original Gerrhety and Roundtree technic was followed: injecting exactly 1 c.c. of the dye intramuscularly and waiting until the dye appeared in the urine before starting the collection of the first one-hour sample which was voided. The bladder was catheterized at the end of the second hour and the percentages estimated by the Dunning colorimeter. In no cases where convulsions occurred was there a normal or near normal reading. The patients who had the lowest percentage dye excretion were clinically the most seriously affected. Mild eclamptogenic toxemias had in some instances normal or above normal readings. A low excretion, less than 15 per cent in two hours is a serious prognostic sign.

Early in the series the eyegrounds were studied in 23 cases. All of the observations were made by ophthalmologists. Of these patients, one presented a mild arteriosclerosis, two a slight edema and sclerosis, and the rest showed no lesion characteristic of serious intoxication. Most of the negative eyegrounds occurred in patients with serious intoxication in whom it was hoped the findings might help to differentiate between the nephritic and preeclamptic toxemia or might furnish an indication for radical intervention. The results were so disappointing that further study was discontinued.

#### INTERFERENCE

Induction of labor was undertaken in two groups of cases: Patients under treatment who failed to respond to medical management, and those who entered the clinic in such serious condition and with a history of such a sudden onset of symptoms that conservative measures seemed contraindicated. Labor was induced by quinine and castor oil in 78 patients. Bag induction was used in 72 cases. The membranes

were ruptured artificially in 110 cases. In some patients all three of these procedures had to be applied to bring about labor. In general, it was noted that bag inductions or rupture of the membranes was necessary in all except those patients who were at or near term or in whom it was evident that an unusual irritability of the uterus made premature labor probable. For this reason in primiparas and especially in elderly primiparas who were not within two weeks of term, cesarean section was frequently the method chosen for delivery to avoid the uncertainties of induction, especially in rapidly advancing toxemias. Rupture of membranes was especially indicated in multiparous patients at term or in the early stages of labor. This procedure was never used when cesarean section was considered as even a remote possibility as the method of delivery. There was no more morbidity than would be expected from an equal number of nontoxic patients delivered in the same way. This speaks against the view of Williams, DeLee, and others that the eclamptogenic woman is especially liable to infection.

Of these 500 patients, 396 were delivered spontaneously which, I believe speaks for itself, as to the conservative attitude toward these cases in our clinic. Forceps were used in 38 cases all of which were midforceps or low forceps. Version and extraction were done 18 times. The indications for these operations were mixed. Only a small percentage were done for the sole indication of toxemia of pregnancy. In most cases an important contributing indication was present, such as a long second stage, rigid perineal muscles, contracted pelvis, cardiac lesions or evidence of maternal or fetal exhaustion.

Cesarean section was done in 25 cases. In practically all of these the most serious types of toxemia that were seen in the entire series were present. We use this method of delivery especially in the patient with a sudden attack of toxemia who is clinically normal in the morning and who may be dead by night with all the signs and symptoms and postmortem findings of eclampsia.

Our conception of the pathogenesis in these cases is that the fetus and placenta are nearly always responsible. A sudden release of toxin overwhelms the defense mechanism. This may be due to infarcts in the placenta as Young thinks. Many patients showing placentas with very extensive infarct formation show absolutely no signs of eclamptogenic toxemia. There may, however, be differences in the kind of infarct or in the speed with which they develop to account for the appearance of toxic symptoms.

In these patients with a fulminating toxemia we do a cesarean section as soon as the necessary preparations can be made. Striking directly in this way at the source of the toxins would seem to be the logical method of approach when proper facilities are available.

An important factor in this connection is a prompt decision as to what should be done and rapid execution of the plan. Delay and temporary conservatism to see whether the convulsions become more frequent or stronger and whether or not they may be controlled by medical management, while successful in many cases will not give as good results in the long run.

The other group of patients who were delivered by cesarean section were the more slowly advancing toxemias who in spite of adequate medical management continue to grow worse and in whom induction of labor from below seems to be contraindicated.

Cesarean section is never the operation of choice in the delivery of a patient with eclamptogenic toxemia, but it may very well be the lesser of two evils when the dangers to both mother and child from further continuance of the pregnancy or a delivery from below are considered.

Local anesthesia or a combination of local and ethylene anesthesia was used in all cesarean operations.



One of the patients who had a cesarean section died of a general peritonitis following a classical operation. She had no convulsions. The operative mortality, therefore, would be 4 per cent in this series of cesarean operations.

The babies of eclamptogenic toxemia patients were found to be, as a rule, less well developed and less vigorous than babies from normal women. The toxic state of the mother reflects itself on the child if present for a long time before the birth of the baby or if it is of very severe grade. Therefore the greatest attention should be paid to the proper conduct of the labor to prevent undue pressure on the babies head and to protect it from shock and exposure as soon as it is born. Frequently the attention of the doctor and nursing personnel is so focused on the condition of the mother that as a result the welfare of the baby may be neglected immediately after birth, much to its detriment. We prepare in each case for the reception of an undernourished, asphyxiated baby that is toxic and in some shock. If there is considerable prematurity, we dilate the perineum manually and do a lateral episiotomy to prevent undue pressure. The use of local anesthesia to block the perineal nerves is of value, since it serves to relax the perineal muscles and decrease pressure on the fetal head. Furthermore it reduces painful stimuli from the stretching perineum, and cuts down very materially the amount of inhalation anesthesia necessary for obstetric analgesia or replaces it entirely.

Careful attention to the premature infant who should be placed in an incubator for at least twenty-four hours is very important. Oxygen is used for blue spells, and the trachea is kept clear of mucus by gentle suction with the tracheal catheter when necessary. Food is a secondary consideration until respiration is satisfactorily established, after which we give small amounts of mothers' milk diluted to half strength and fed by a medicine dropper or gavage as the strength and aptitude for feeding of the infant seems to indicate.

Failure to recognize the precarious condition of these toxic premature babies has, we feel, resulted in the unnecessary loss of a considerable number of lives.

There were 66 fetal deaths in the series. Of these, 38 were babies from mothers with a diagnosis of eclamptic and preeclamptic toxemia and 28 were babies from mothers with a nephritic toxemia. Twenty-five of the 66 babies were born alive and died before leaving the hospital. All babies that went home with their mothers were in good condition on leaving the hospital.

The cause of death was the toxemia in eight cases as nearly as could be determined. The cause of death in one other case was cord hemorrhage and syphilis. Of the babies born dead 25 were stillborn without maceration, 23 were macerated, 15 were under 2,000 gm., 2 were marked deformities or monstrosities. There was a gross fetal mortality of 11.2 per cent. The corrected fetal mortality in babies over 2,000 gm. who died from no other obvious cause than toxemia was 1.6 per cent. Twelve babies who were born alive and died were from mothers classified as eclamptic or preeclamptic, giving a mortality for this group of 2.2 per cent; of the 12 only 4 were viable babies. The cause of death in all was atelectasis and pneumonia as shown by postmortem examination. Only 4 of the 12 babies were over 2,000 gm.

Of the babies from nephritic toxemic mothers, 13 were born alive and died, a mortality of approximately 40 per cent. Only 4 of the 13 babies were over 2,000 gm.

The Wassermann test was found to be positive in only 4.6 per cent of 418 cases. This is relatively low, for in normal pregnant women we found it to be 13.6 per cent in a similar group of cases (Falls and Moore).

Of the 500 cases of eclamptogenic toxemia, 403 were preeclamptic according to the Williams classification, 29 were eclamptic and 68 were nephritic. We recognize the pitfalls in attempting to classify cases in this manner from clinical evidence, but the classification was made only after careful prenatal history and postnatal observa-

tion. It was found impossible with the facilities at our command to follow up each case over a period of months and years to help determine the classification to which it should belong.

Two of the women in this series died. Neither of these patients had gone on to the convulsive stage. Viewing the cases in retrospect, it would seem that those deaths occurred from failure to adhere rigidly to the scheme of treatment herein outlined.

#### FATALITIES

CASE 1.—M. C., a thirty-three-year-old colored para x, was in the hospital from Feb. 3, 1931 until Mar. 4, 1931. She entered with a pressure of 190/115. Because of the borderline viability of the baby she was treated conservatively for twenty-five days when, because of increasing epigastric pain, headache and edema, a classical cesarean section was done and sterilization performed. The operation lasted forty-seven minutes, the postoperative condition was good. She had no postoperative convulsions.

Postmortem examination revealed: Generalized peritonitis, extreme fatty degeneration of the liver with no areas of focal necrosis; early arteriosclerosis and arteriosclerosis of the kidney with marked fatty degeneration, and early bronchopneumonia.

CASE 2.—A white primipara, thirty-four years of age, was sent into the hospital for observation Oct. 4, 1933 and delivered Oct. 18, 1933. She was first seen in the dispensary Sept. 5, 1933 and had no albuminuria or elevation of the blood pressure; on Sept. 18, 1933 she had a blood pressure of 152/102 and was advised as to diet and rest at home. At this time the urine showed a faint trace of albumin. On admission she was found to have a blood pressure of 166/104 and came into the hospital. On October 7 the blood chemistry showed nonprotein nitrogen 32, creatinine normal, and  $\text{CO}_2$  combining power 48.

Following spontaneous labor and delivery she was apparently normal in every way. Three hours later she had a severe postpartum hemorrhage and went into shock. Stimulants were ordered, 1,500 c.c. of 5 per cent glucose and normal saline hypodermically caused a temporary improvement. She died in shock about fourteen hours after delivery.

The postmortem examination showed anemia of the parenchymatous organs, hemorrhage into the trachea and bronchi, petechial hemorrhages into the renal pelvis, generalized arteriosclerosis, fibrous adhesions of the pleura, and adenoma of the pancreas.

Microscopically the kidney findings were those of a toxic nephritis.

The liver findings showed no areas of thrombosis or necrosis.

Since similar cases clinically have shown hypoglycemia, blood was taken at autopsy which showed a glucose reading of 140 mg. per 100 c.c.

#### SUMMARY

The analysis of these cases serves to bring out certain points for consideration in connection with the etiology and treatment of this disease. Solomons has rightly said that if theories are to be of any use they must assist in determining suitable clinical treatment. We might go further and say that if a treatment based on a theory results in the marked reduction of the incidence, mortality, and morbidity of the disease, it helps to prove the correctness of the theory.

It is a significant fact that in Chicago in the same general grade of patient, with about the same type of hospital care, the mortality on the north side of Polk Street is between 16 and 20 per cent in the convulsive group, and on the south side of the street in the same block, there is no mortality in the same group. This is not due to superior knowledge or skill of the attending staffs of the two institutions, but to the smaller number of cases affording closer supervision and more attention to detail of management in the second institution, both before and after entry into the hospital.

That the mortality in a group of toxic women by careful handling can be brought down to the figure for pregnant women in general in well-conducted clinics is thought-provoking.

The fact that a disease which has for years held a mortality of from 20 to 30 per cent can be so controlled that there are not enough cases of the convulsive type in from twelve to fourteen hundred patients a year to demonstrate to the student convulsions or patients who have had convulsions, is important, especially when we remember that this type of intoxication is one of the most important of the causes of maternal mortality in the United States today.

Finally, it is important to note that this reduction in mortality and in the incidence of the convulsive stage of the disease is decreasing not only in one clinic but all over the country where adequate prenatal care is given.

There is, therefore, no excuse for the development of serious eclamptogenic toxemia except the ignorance or slothfulness of the physician and patient in applying what is already known to the control of the disease.

It is our duty to continually reiterate these facts to our students, to the medical profession, and to the laity, to the end, that this preventable malady will cease to take its annual toll.

#### CONCLUSIONS

1. Eclamptogenic toxemia can be controlled in most cases by reducing the amount of protein split products in the blood and increasing elimination by the bowel.
2. When the symptoms do not yield to conservative management, the uterus must be emptied.
3. Cesarean section is indicated in patients with fulminating toxemia or when induction of labor or delivery from below is contra-indicated.
4. Eyeground examination is of little value as an aid in determining the severity of a given case.
5. The phenolsulphonephthalein test is of value prognostically.

6. Treatment should be continued postpartum until the symptoms have definitely improved to reduce the incidence and severity of postpartum convulsions.

7. Sedatives, intravenous magnesium sulphate injections, and intravenous glucose injections, while rational and in some cases helpful, are not essential as part of the antepartum treatment.

8. Patients first seen in labor are usually best delivered from below.

9. Elderly primiparas near term but not in labor are best delivered by cesarean section because of the danger and uncertainty of delivery by induction of labor.

10. There is no advantage in dividing these cases into eclampsia, low reserve kidney, preeclampsias, and eclampsism.

11. Because of the prematurity and toxic condition of the babies in these cases extra precautions must be taken to insure their safety during labor and in the first days thereafter.

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30 NORTH MICHIGAN AVENUE

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Klaften, E.: The Treatment of Leukorrhea and Erosions by Vaginal Application of Insulin, Med. Klin. 50: 571, 1934.

During the last few years Klaften has been treating erosions of the cervix, ulcerations of the vagina and intractable leucorrhea by means of the local application of insulin. The author compared two series of cases of cervical erosion. In one he injected insulin hypodermically daily and in the other he applied insulin locally. Both series of women were on a high carbohydrate diet and in both series the cervical erosions cleared up. In diabetic women with cervical erosion, leucorrhea and pruritus of the vulva, improvement or cure was obtained in ten to fourteen days. The disappearance of the vaginal discharge runs parallel with the improvement in the diabetes and in some cases, return of the vaginal discharge was a forerunner of aggravation of the diabetic condition. Good results were also obtained in cases of nonspecific vaginitis and leucorrhea. This was especially apparent in cases where the customary local treatment failed to bring about improvement. In addition to the local applications of insulin, the patients were placed on a high carbohydrate diet and abundant calcium.

The good effects of insulin are due partly to the absorption of insulin into the general system and partly to the local effect which induces an increase in the glycogen content of the vaginal epithelium. The vaginal flora, however, is not affected by insulin.

J. P. GREENHILL.

# FIVE-YEAR RESULTS IN FIFTY-SIX CASES OF CARCINOMA OF CORPUS UTERI\*

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FROM Jan. 1, 1921, to Sept. 30, 1929, 56 patients with corpus uteri carcinoma were treated by Dr. H. S. Crossen and myself. The series included our private and ward cases in the Gynecological Service of the Barnes Hospital and Washington University Medical School.

In analyzing this group of cases, we have followed closely, plans laid down by Healy and Cutler in 1930. In this work we have devoted especial attention to two problems: first, the relationship between histologic structure and prognosis and, second, the comparative value of radiation and operation in the treatment of these growths. It is our purpose, therefore, to study the various factors which influence the ultimate result, as a help in determining the treatment of choice of each histologic type of corpus carcinoma. Until recent years these cases have been classified simply as carcinoma of the corpus uteri, no attempt being made to separate the different grades of carcinoma.

In our analysis we have followed the classification of Mahle, later confirmed by Healy.

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|-----------|--|
| Grade I   | Superficial papillary adenoma malignum |
| Grade II  | Adenoma malignum                       |
| Grade III | Adenocarcinoma                         |
| Grade IV  | Diffuse (anaplastic) carcinoma         |

*Adenoma Malignum (Grade II).*—Of fifteen patients belonging to this group treated five years or more ago (Tables II, III, IV) seven were treated by hysterectomy alone. Five are alive five to six years after treatment. Two are dead. One died on the fourth day following operation from peritonitis and the other one died on the tenth postoperative day from bronchopneumonia. Five patients were treated by combined hysterectomy and radiation. Three are alive five to ten years after treatment. One died one and one-half years after treatment from recurrent cancer and the other one was living four years after treatment but then was lost in follow-up, hence considered as dead, although she may be alive. Three patients were treated by radiation alone. None survived five years. Two died of cancer. Cause of one death unknown.

\*Read at the Forty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 6, 7, and 8, 1934.

In this series all the slides showing grading as to type of growth were reviewed by Dr. O. H. Schwarz, who has taken special interest in these pathologic problems.

TABLE I. PAPILLARY ADENOMA MALIGNUM GRADE I

CASE	AGE	NO. PREG.	DURATION SYMPTOMS	OPERATION AND DATE	MG. HR. RADIUM DATE GIVEN	SERIES X-RAY	ALIVE	DEAD	REMARKS
11	70	0	3 mo.	-----	2400 8/6/23	2	11 yr.		Uterus normal size. 8/1/34 no cancer.
24	33	0	5 mo.	Complete hysterect. 4/7/25	None	1	9 yr.		Curettings showed sup. pap? adenoma malignum. 8/1/34 no cancer.
26	49	4	2 yr.	Complete hysterect. 5/28/25	None	None	9 yr.		Uterus enlarged. 4/5/34 no cancer.
54	37	4	2 mo.	Supravag. hysterect. 8/20/29	None	1	5 yr.		Cancer was not suspected. Op. was for enlarged uterus. 7/1/34 no cancer.

TABLE II. ADENOMA MALIGNUM GRADE II. TREATED BY HYSTERECTOMY ALONE

CASE	AGE	NO. PREG.	DURATION SYMPTOMS	OPERATION DATE	ALIVE	DEAD	REMARKS
32	58	3	2 mo.	8/12/26		4 days	Curettings showed adenoma malignum. Died four days after operation. Peritonitis.
43	60	0	1 yr.	3/23/28	6 yr.		No curettage. 4/6/24 no cancer.
45	48	4	2 mo.	6/19/28	6 yr.		Uterus enlarged. 7/1/34 no cancer.
46	49	3	3 mo.	8/ 6/28	6 yr.		Curettings showed adenoma malignum. 7/14/24 no cancer.
47	38	0	None	10/ 6/28	6 yr.		Uterus enlarged. Myoma and ad. malig. Sup. vag. hysterect. 9/1/34 no cancer.
48	60	0	6 mo.	10/24/28		10 days	Died ten days after operation of bronchopneumonia.
49	49	0	1 yr.	3/12/29	5 yr.		No curettage. 7/24/34 no cancer.

*Adenocarcinoma (Grade III).*—Of twenty-seven patients belonging to this group, treated five years or more ago (Tables V, VI, VII), six were treated by hysterectomy alone. Four have survived five to eleven years. Two were lost in the follow-up and considered as dead. Fourteen patients were treated by combined hysterectomy and radiation. Nine are alive five to thirteen years after treatment. Five died within three years after treatment, four from cancer and one committed suicide because she had cancer. Seven patients were treated by radiation alone. One has survived five years and six died within four years after treatment.

*Diffuse (Anaplastic) Carcinoma (Grade IV).*—Of ten patients belonging to this group, treated five years or more ago (Table VIII), three are living six to eight years after treatment. Two were treated by combined hysterectomy and radiation and one by vaginal hysterectomy alone. Seven are dead, one died from postoperative

TABLE III. ADENOMA MALIGNUM GRADE II. TREATED BY COMBINED HYSTERECTOMY AND RADIATION

CASE	AGE	NO. PREG.	DURATION SYMPTOMS	OPERATION DATE	MG. HR. RADIUM DATE GIVEN	SERIES X-RAY	ALIVE	DEAD	REMARKS
7	51	1	1 mo.	11/14/21	None	1	6 yr.		Curettings showed adenoma malignum. Died 8/24/27, cause not cancer.
16	55	0	2 mo.	8/12/24	None	3	10 yr.		Myoma and adenoma malignum. Cancer not suspected. Sup. vag. hysterect. 7/1/34 no cancer.
30	54	2	6 mo.	10/ 3/25	None	3		1½ yr.	Died of recurrent cancer April, 1927.
35	49	0	1 yr.	12/ 3/26	1600 11/26/26	None	5 yr.		Uterus enlarged. Curettings showed adenoma malignum. 3/2/32 no cancer.
52	53	0	2 yr.	4/29/29	None	1		4 yr. ?	Cancer not suspected. Operation was for myoma. 1/1/31 no cancer.

TABLE IV. ADENOMA MALIGNUM GRADE II. TREATED BY RADIATION ALONE

CASE	AGE	NO. PREG.	DURATION SYMPTOMS	MG. HR. RADIUM DATE GIVEN INTRA-UTERINE	SERIES X-RAY	ALIVE	DEAD	REMARKS
15	60	3	2 yr.	3000 6/23/24	4		3 yr.	Enlarged uterus. Curettings showed Ad. Mal. Died 8/6/27, cause unknown. Last exam. 1927 no cancer.
36	42	3	3 yr.	3000 12/ 9/26	3		10 mo.	Enlarged uterus. Far advanced cancer. Died 8/23/27 of cancer.
51	48	0	1 yr.	3600 4/11/29 2500 7/ 2/32	2		3½ yr.	Large mass protruding from uterine canal. Ad. malignum. Cancer present 3 yr. after first radium. 8/24/32 last information. Probably died of cancer.

TABLE V. ADENOCARCINOMA GRADE III. TREATED BY HYSTERECTOMY ALONE

CASE	AGE	NO. PREG.	DURATION SYMPTOMS	OPERATION DATE	ALIVE	DEAD	REMARKS
2	58	2	6 mo.	4/ 9/21	11 yr.		Curettings showed adenocarcinoma. 9/1/32 no cancer.
9	41	4	2 yr.	4/26/23	11 yr.		Enlarged uterus. Myomas and adenocarcinoma. 8/1/34 no cancer.
10	58	2	8 mo.	8/ 4/23		?	Lost in follow-up. Never returned after operation.
22	54	6	1 yr.	2/20/25	9 yr.		Curettings showed adenocarcinoma. 3/3/34 no cancer.
39	63	3	2 yr.	6/21/27		?	Lost in follow-up. Never returned after operation.
53	50	0	1 yr.	5/30/29	5 yr.		Enlarged uterus. Myoma and adenocarcinoma. 7/1/34 no cancer.

pneumonia on the fifth day following operation, and six died from cancer within one and one-half years after treatment. All of these cases were far-advanced carcinoma and the treatment given was mostly palliative.

*Age Incidence.*—The following is the distribution of corpus uteri carcinoma according to age: thirty to forty years, 4 cases; forty to fifty years, 15 cases; fifty to sixty years, 21 cases; sixty to seventy years, 13 cases; seventy to eighty years, 2 cases; eighty to ninety years, 1 case. The greatest number of cases occurred between the ages of fifty and sixty years. The second decade having most cases was forty to fifty years, and the third was sixty to seventy years. The youngest patient in our series was thirty-three years of age, and the oldest was eighty-one years of age.

*Effect of Gestation.*—Twenty of the patients were nulliparas, 4 were primiparas, 28 were multiparas, and 4 were unclassified.

*Symptoms.*—The average duration of symptoms in the entire series from time of onset to time of admission was twelve months. The outstanding clinical symptom is vaginal bleeding. Pain is a late manifestation of the disease.

#### CONCLUSIONS

The final discussion as to which is the best method of treatment for each of the several grades of carcinoma of the corpus must rest upon a large accumulation of reliably reported five-year results with the various methods. This detailed report is a contribution to such necessary accumulation. An additional item which should be included in such reports, is an accurate statement of the extent of the gross pathology in the specimen removed at operation. In this early series such information was lacking in a considerable proportion of the cases, but in later cases the gross findings in the specimen are recorded in detail, along with the microscopic findings. Such recording of the extent of the lesions in the structures removed, along with an accurate description of the clinical findings at examination and during operation or radium implantation, will enable more accurate classification of reported cases.



TABLE VI. ADENOCARCINOMA GRADE III. TREATED BY COMBINED HYSTERECTOMY AND RADIATION

CASE	AGE	NO. PREG.	DURATION SYMPTOMS	OPERATION DATE	MG. HR. RADIUM DATE GIVEN	SERIES X-RAY	ALIVE	DEAD	REMARKS
4	58	3	1 yr.	10/ 1/21	None	1		2 mo.	Patient committed suicide shortly after being treated.
5	61	2	?	10/28/21	1125 10/ 2/21	None	7 yr.		Enlarged uterus. Curettings showed adenocarcinoma. 9/27/28 no cancer.
6	54	0	3 yr.	11/ 3/21	1200 10/26/21	None	13 yr.		Enlarged uterus. Curettings adenocarcinoma. 7/1/34 no cancer.
12	46	3	8 mo.	11/14/23	1745 9/12/23 1453 9/18/23	None	5 yr.		Curettings adenocarcinoma. Uterus removed showed no cancer. 10/10/28 no cancer.
14	44	0	1 yr.	1/ 3/24	None	3		3 yr.	Myoma and adenocarcinoma. 1927 died of cancer.
18	53	0	3 yr.	7/30/24	None	2	5 yr.		Curettings adenocarcinoma. 5/27/29 no of cancer.
19	62	3	5 mo.	8/14/24	None	1	10 yr.		Enlarged uterus. Curettings adenocarcinoma. 9/1/34 no cancer.
23	58	0	?	4/ 4/25	None	1		1 yr.	Curettings adenocarcinoma. Enlarged uterus. 9/8/26 died of cancer.
25	48	0	6 mo.	4/24/25	None	2		1 yr.	Uterus small. Curettings adenocarcinoma. 5/24/26 died of cancer.
28	69	3	5 mo.	8/13/25	None	1	9 yr.		Enlarged uterus. Curettings adenocarcinoma. 8/1/34 no cancer.
34	57	1	6 mo.	11/20/26	1800 10/28/26	None	8 yr.		Curettings adenocarcinoma. 4/23/34 no cancer.
40	76	0	2 yr.	11/23/27	None	1	6 yr.		Enlarged uterus. Curettings adenocarcinoma. 7/25/33 no cancer.
55	51	3	?	9/ 5/29	None	1		3 yr.	Myoma and adenocarcinoma. Cancer not suspect. 11/1/32 no cancer.
56	42	0	3 yr.	10/17/29	2400 9/ 1/29	2	5 yr.		Myoma and adenocarcinoma. Curettings adenocarcinoma. 7/1/34 no cancer.

TABLE VII. ADENOCARCINOMA GRADE III. TREATED BY RADIATION ALONE

CASE	AGE	NO. PREG.	DURATION SYMPTOMS	MG. IIR. RADIUM DATE GIVEN INTRA-UTERINE	SERIES X-RAY	ALIVE	DEAD	REMARKS
3	62	3	1 yr.	1350 6/27/21	2		4 mo.	Enlarged uterus. Advanced cancer. Last information 8/26/21 not well.
13	62	?	2 mo.	None	1 12/ 4/23		?	Advanced cancer. Curettings showed adenocarcinoma. Died shortly after treatment.
21	57	0	2 yr.	None	2 2/14/25		?	Advanced cancer. Curettings showed adenocarcinoma. Died shortly after treatment.
29	66	1	1 yr.	1800 9/ 7/25 1000 10/ 7/25	1		2 mo.	Advanced cancer with heart disease. Uterus large. 11/13/25 died of heart disease.
31	81	0	6 mo.	1000 11/21/25 2000 12/ 7/25	1		4 yr.	Curettings showed carcinoma. 7/6/29 died of senility.
41	56	2	1 yr.	None	1 12/23/27		2 yr.	Enlarged uterus. Advanced cancer. 1/13/30 died of cancer.
50	64	7	?	2500 4/ 6/29	2	5 yr.		Uterus small. Curettings showed adenocarcinoma. 4/30/34 no cancer.

In comparing the results of different methods of treatment for any grade of corpus carcinoma, the comparison should be made with cases of the same approximate extent, i.e., early cases to early cases and late cases to late cases. Otherwise there may be erroneous conclusions as to the efficacy of the different treatment methods. This point is illustrated by this series, in which death resulted in nearly all patients receiving only radiation treatment. Thus the general results would indicate that radiation has very little effect toward cure. But when the extent of the disease is looked into, we find that practically all cases presenting reasonable hope of cure were subjected to operation, radiation alone being limited to the hopeless cases. Hence the results do not show the relative efficacy of radiation even of those days, and much less of the improved radiation of the present.

Basing our decision on subsequent five years of experience along with the experience with the cases reported, we feel at present that operation plus radiation is the safest plan of treatment for carcinoma

TABLE VIII. DIFFUSE (ANAPLASTIC) CARCINOMA GROUP IV

CASE	AGE	NO. PREG.	DURATION SYMPTOMS	OPERATION AND DATE	MG. HR. RADIUM DATE GIVEN	SERIES X-RAY	ALIVE	DEAD	REMARKS
1	38	2	3 yr.	Supravag. hysterect. 1/9/21	None	None		1 mo.	Far advanced cancer. Feb., 1921, died of cancer.
8	64	7	1 yr.	Explorat. lap.	1800 4/ 1/22	None		?	Advanced cancer. Died shortly after treatment.
17	57	1	1 yr.	None	3000 7/ 5/24	None		13 days	Advanced cancer. 7/18/24 died of cancer.
20	61	5	2 yr.	None	3000 11/ 3/24	2		1 yr.	Curettings cancer. 11/13/25 died of cancer.
27	48	?	1 yr.	Supravag. hysterect. 8/1/25	2000 7/ 6/25	1		1½ yr.	Curettings cancer. Received some radium elsewhere. 2/17/27 died of cancer.
33	43	?	?	Supravag. hysterect. 9/1/26	None	None		5 days	Cancer not suspected at time of operation. 9/6/26, died of pneumonia.
37	57	3	3 yr.	Vaginal hysterect. 12/17/26	None	None	8 yr.		Cancer not suspected at time of operation. 9/1/34, no cancer.
38	56	11	1 yr.	Supravag. hysterect. 3/10/27	None	None		?	Enlarged uterus. Died shortly after operation.
42	54	0	4 mo.	Complete hysterect. 12/23/27	None	2	6 yr.		Enlarged uterus. Inoperable. 9/28/33, died of cancer.
44	61	3	1 mo.	Complete hysterect. 5/24/28	None	1	6 yr.		Curettings cancer. 9/1/34, no cancer.

TABLE IX. NUMBER OF FIVE-YEAR CURES IN DIFFERENT GRADES BY DIFFERENT TREATMENTS

	HYSTERECTOMY ALONE					HYSTERECTOMY AND RADIATION COMBINED					RADIATION ALONE					TOTAL TREATED 5 YEARS AGO
	GRADE I	GRADE II	GRADE III	GRADE IV	TOTAL	GRADE I	GRADE II	GRADE III	GRADE IV	TOTAL	GRADE I	GRADE II	GRADE III	GRADE IV	TOTAL	
Number patients treated 5 yr. ago	3	7	6	4	20		5	14	4	23	1	3	7	2	13	56
Alice 5 to 13 years after treatment	3	5	4	1	13		3	9	2	14	1		1		2	29
Died after treatment		2		3	5		2	5	2	9		3	6	2	11	25
Lost, unable to locate			2	0	2				0	0						2
Total	3	7	6	4	20		5	14	4	23	1	3	7	2	13	56

of the corpus uteri. If the patient is a good operative risk, hysterectomy of a type suitable for this disease is carried out. Such hysterectomy is supplemented by radiation to devitalize any cancer cells which may be beyond the structures removed. This may be given before or after the operation or both, and may be given by means of radium or x-ray or both. If the patient is a poor operative risk, the treatment to be employed is determined by a careful consideration of the seriousness of the contraindication to operation and of the efficacy of radiation in a growth of that particular type and extent.

WALL BUILDING

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## INTRACTABLE DYSMENORRHEA\*

### RELIEF BY SYMPATHETIC NEURECTOMY

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**Q**UI *dolorem vincit, humanitati servit*. The recent developments in sympathetic nerve surgery in its relation to relief of pain have given us added opportunities to serve humanity in this respect. The relief afforded women suffering from dysmenorrhea following excision of the superior hypogastric sympathetic nerve plexus (presacral nerve) seems to indicate, when compared with the amelioration of pain afforded in other conditions which cause pelvic pain, that it is in dysmenorrhea that sympathectomy will be of outstanding value. This statement is made as a result of personal observations, and recent reports by American colleagues.<sup>1</sup> The experience in this country closely parallels that of European surgeons.

The anatomy and technical surgical procedure has been so well and repeatedly described in recent literature,<sup>2</sup> both in this country and abroad, that only a brief summary is here presented, including a discussion of technical points to be observed. I have operated upon three women with primary (spasmodic) dysmenorrhea, and upon several in whom there was a mild dysmenorrhea (secondary, congestive type), in whom the operation was done as an added procedure during the course of other pelvic work. Although the latter group of patients have had comfortable menstrual periods since the operation, I am reporting here only the three patients in whom the operation was performed primarily for the relief of dysmenorrhea of a severe type. One of these women has since had a baby. Her obstetric history is given in detail.

\*Read at the Forty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 6, 7, and 8, 1934.

Recent reports in American literature indicate that the operation has been done rather extensively, and that there is always a mortality rate in abdominal operations, even though it be low, must be kept in mind. It is for that reason that I feel the operation should be limited to the more severe types of dysmenorrhea. Of course, if at the insistence of the patient, and because of the individual patient's unstable nervous system, with the resultant magnification of symptoms plus the inevitable economic features such as loss of position, disturbance of familial relationship, etc., one may be forced to accept the risk.

Severe dysmenorrhea has until recently, and as a last resort, been treated by either hysterectomy, radiation therapy, or opiates. Section of the sympathetic plexus has had no deleterious after-effects, which might militate against employing this procedure in young women, when the operation is properly performed. There has been no difference in libido, nor has it interfered with subsequent pregnancy or delivery. When considered in this light it must appeal to the gynecologist as a method preferable to anything which has been at his command before sympathectomy was promulgated as a relief measure.

#### TYPES OF DYSMENORRHEA TREATED

The terms "primary" or "spasmodic," and "secondary" or "congestive," "dysmenorrhea," are made use of in this discussion. By the former we mean that condition in which there is an entire absence of gross pathologic lesions in the pelvis, and in which the pain begins just before or with the appearance of menstruation; and the second in which there is some gross pathologic lesion accompanying the menstrual disturbance and in which the discomfort begins some days before the beginning of the period. The pain in the former group is in the majority of cases much more severe and more disabling than in the latter.

Practically everything in the armamentarium of the gynecologist has been tried for the relief of primary dysmenorrhea, and many theories have been advanced as to its cause. The multiplicity of drugs, and formerly, the numerous operations performed for the relief of dysmenorrhea, is evidence of lack of specificity. This is also true in the matter of the endocrines, for although some cases have responded for a time, many of these patients have eventually had a recurrence of symptoms. The hypoplastic, underdeveloped uterus may be a factor in the etiology because of the disturbed circulation at the time of menstruation. As shown in Case 3 there is a definite possibility that sectioning of the sympathetic nervous supply may improve the circulation, and secondarily cause an increase in the size of the uterus.

The antispasmodic effect of atropine is well known, and it should be remembered that this result is achieved by action on the sympathetic nervous system. Atropine, too, has been our most useful drug in the treatment of dysmenorrhea. This point is interesting because of the fact that the operation under discussion severs most of the sympathetic nerves in connection with the uterus. That pain impulses are conducted through the superior hypogastric plexus is a well-recognized fact. Sectioning of these fibers, therefore, should relieve pain emanating from the uterus whether it be the result of muscle spasm or arterial contractions. Vasospasm *per se* causes pain. Sympathetic nerve sectioning relieves this spasm in peripheral arterial disease, and if such spasm is a factor in dysmenorrhea, some of the relief might be explained on this basis.

It might be that we are seeking a cause in the uterus itself; whereas, it may be quite possible that incident to the congestion accompanying menstruation, there is a stimulation of hypersensitive nerve fibers, some of which may be directly concerned with the conduction of pain impulses.<sup>3</sup> The development of such an hypothesis has interesting possibilities relative to the further study of etiologic factors. In only one case did the pathologist report evidence of inflammatory change in the nerve tissue. This of course might be a factor, and might be discovered only by careful serial sectioning of the entire plexus. It must be kept in mind, however, that sympathetic nervous systems vary as do individuals, and one system might be more prone to react to slight insults than another. Most women with dysmenorrhea fall into the group of "sympathetico-tonics," which adds interest to the speculation that we may be dealing with a disturbance of normal balance, with a hypersensitive uterine sympathetic nervous mechanism, and that agitation of the same at the menstrual period, eventuates in painful overactivity.

#### ANATOMY AND OPERATION

The surgical anatomy of the so-called presacral nerve, better known as the superior hypogastric plexus (it does not lie in front of the sacrum), has been well described by Elaut.<sup>4</sup> Cotte,<sup>2</sup> and Fountaine<sup>5</sup> have discussed the operation, the former having developed the technic as it stands today.

The completeness of the contributions of these men make it unnecessary to do more than briefly recall a few salient points.

The superior hypogastric plexus lies in a region quite familiar to the pelvic surgeon. He needs but to pick up the posterior parietal peritoneum overlying the triangle formed by the bifurcation of the aorta, incise this layer, and thus find the area containing the plexus. In some cases the mesosigmoid is implanted to the right of the midline. This adds difficulty to the procedure, for vessels must be spared. In these cases I have found that a small nick in the right leaf, followed

by gentle tearing of the peritoneum is of great assistance in the avoidance of vessel injury. In the ordinary case, of course, a longitudinal incision is made with the scissors. This should extend about an inch above the bifurcation of the aorta, and downward to the level of the sacral promontory. A long peritoneal incision facilitates retraction laterally, and materially aids exposure. Repeatedly drying the area with a gauze sponge aids in the definition of the finer strands, which are often no larger than a thread in a spider web. This is particularly true in the lateral areas, where communicating fibers from the intersigmoid plexus, and from the lower lumbar sympathetic chain are to be found. It is quite likely that failure to pick up some of these small fibers has been the reason for a few reports of unsatisfactory results.

At the lower end of the plexus two distinct bundles of nerve fibers may be seen: the hypogastric nerves. It is here that care must be exercised. When cutting through the lower plexus fibers, no part of these bundles should be included, for it is quite likely that inclusion of extensive pieces of the hypogastric nerves may be the cause of bladder disturbances.

The usual midline incision is made but may well be extended for a short distance above and to the left of the umbilicus. The bowel should be well emptied by saline enemas, thus materially aiding the necessary "packing away" of the intestines, so essential to good exposure of the area attacked. Spinal anesthesia aids materially in this essential. The fibers of the plexus are best picked up by means of a small blunt hook. Palpation of the two common iliac arteries at the bifurcation of the aorta materially assists in the location of the area, and indicates the point where the fibers are most readily seen. A small dental cotton pledget on a long forcep or hemostat is a useful instrument for teasing out the fibers. Fibers should be definitely identified. Often the main group of strands lies close to, or even slightly under, the left common iliac artery, and this must be kept in mind if a complete dissection is to be made.

#### CASE HISTORIES

CASE 1.—Mrs. F. M., aged twenty-five, occupation, office clerk. Her chief complaint was severe dysmenorrhea since the beginning of menstruation at the age of thirteen, and dyspareunia since her marriage in August, 1933. She had regular twenty-eight-day periods of four days' duration. Cramps always began about two hours before the beginning of the menstrual flow, and were of terrific severity for four hours, after which the patient was exhausted. Her lower abdomen remained sore for five days, and she was unable to work during that time. Vomiting occurred synchronously with the cramps. Her general health had been good and she had never had a serious illness. All the usual medical treatments had been of no avail. Physical examination disclosed a well-nourished young woman with no evidence of pathologic conditions. It was difficult to examine her vaginally as the introitus was small, and extremely sensitive. She was very anxious for relief, for she was in danger of losing her position as the result of repeated absence from work.

She was operated upon April 30, 1934, at which time the uterus was found to be normal in size, and the ovaries and tubes normal. There were no adhesions in the pelvis. The appendix was tightly bound down in a retrocecal position, and was removed with some difficulty. The superior hypogastric sympathetic nerve plexus was then excised.

One week after the operation the patient menstruated and had absolutely no pelvic discomfort. Quite naturally, she was delighted, and it was the first time



during her menstrual life that this had occurred. Her postoperative course was entirely uneventful. Recent follow-up shows that this relief has continued, and she loses no time from work. There is no dyspareunia.

CASE 2.—Mrs. A. E. H., aged twenty-three, stenographer. Began menstruating at the age of twelve, and continued to menstruate at five-week intervals until a few months before the present examination on June 9, 1933, at which time she began menstruating every twenty-eight days and had five-day periods of a moderate amount. She had always had severe cramps for about two hours, at the beginning of each period. In 1931 she was practically free from dysmenorrhea, but in the middle of 1932 the cramps, which had begun early in the year, became increasingly severe until, as she described it, she was in agony all of the first day and usually had to stay in bed about three days. The pains, however, lasted for the entire five-day period. There had been no previous serious illnesses. It was interesting to note that her mother died of apoplexy at fifty-two, and that she had also suffered from dysmenorrhea. This patient had employed several physicians, and had been given all of the usual medical care without benefit. She finally employed an osteopath, and then at the end, a chiropractor. She was in great danger of losing her position.

At operation no pathologic condition was found in the pelvis. The superior hypogastric plexus was resected under spinal anesthesia. Following the operation there was difficulty in urinating, and it was necessary to catheterize her for about three days. Then for about three days she had a marked urinary frequency. This gradually disappeared and bladder function was normal in ten days. She had always been constipated and was in the habit of taking cathartics. Following her operation her constipation gradually disappeared until, at the present time, her bowels move normally. This effect is in keeping with the results reported in relation to the relief of constipation in individuals whose superior hypogastric plexus had been removed for the cure of that condition. The first period after the operation occurred in five weeks. This delay upset her somewhat and, as she stated when her menstruation began, she had a tingling sensation in both hip regions which made her fear that she was going to have cramps so she went to bed. No cramps occurring, however, she got up and did a half day's baking. Since then she has had a disturbing backache at the time of her periods, but no pelvic pain, and is able to continue with her work. She had been told that the operation would cause frigidity. This, she states, has not occurred.

CASE 3.—Mrs. P. L., aged twenty-six, a nurse. This case has been previously reported in the *Journal of the American Medical Association* (101: 1295, 1933). An error occurred in the case history as then reported, and should be noted at this time. It was stated that, "the uterus was normal in size," whereas it should have read, "the uterus was subnormal in size." This woman had had dysmenorrhea since she began to menstruate at the age of fourteen. Her periods had always been scanty, and for the two years preceding the time that she consulted me, there had been a gradual increase in the severity of her dysmenorrhea. She was unable to work, sometimes for two weeks, the disturbance toward the end having made it necessary for her to stay in bed nearly three weeks. She was very obese, being eighty pounds overweight. No medical treatment was of avail, and her physician at times had to resort to morphine. As previously reported, both ovaries were markedly sclerotic and the left one was removed, the right one being partially resected, a piece approximately one inch long, one-half inch wide, and one-quarter inch thick being left along the hilus. This patient menstruated regularly and without pain until thirteen months after her operation. She was sent to me in May,

1934, more than a year and a half later. Her physician felt that she might have a large ovarian cyst, or that she was pregnant. A diagnosis of pregnancy was made.

She was delivered of a living child on Aug. 15, 1934. Her first stage was conducted under morphine and scopolamine and lasted approximately eighteen hours. The pains were irregular and weak, and were mostly in the nature of a backache. She had no pains in front. The position was right occiput posterior. Her second stage lasted between four and five hours, and the head rotated to an occiput posterior position. Her physician (Dr. E. J. Dillon, Phoenix, N. Y.), called in an obstetrician (Dr. R. J. Pieri, Syracuse, N. Y.), who found that the head was not down on the perineum. Under ether anesthesia a Scanzoni midforceps operation was performed. Both physicians noted the unusual relaxation of the perineum, and the obstetrician found it unnecessary to iron out the perineum. The babe weighed 8½ pounds. The patient made a perfect recovery following delivery. This case is interesting from several standpoints: first, the period of sterility during her four years of married life; second, the hypoplastic, underdeveloped uterus; third, the labor pains during the first stage, which were observed by her physician throughout the period. While merely conjecture, it is nevertheless interesting to speculate on the effect of section of the sympathetic nerve supply and its relation to increased nourishment secondary to vasodilatation of the uterine vessels. This case shows well the conservative nature of the operation, in that complete ovarian function was preserved even though only a small slice of ovary remained. Not long ago either radiation or hysterectomy would have been employed in this case, for the condition of the patient was pitiful. It also answers well the question which has often been asked as to the effect on pregnancy. Other authors have stated that childbearing was not interfered with and the only effect noted was that low forceps delivery was demanded more than usual.

#### RESULTS

In Case 1 the relief of symptoms was complete, but in the other two there was a complaint of backache and a feeling of discomfort in both hip regions. It is easy to conceive that with relief from the extremely severe cramps, the other aches would be more noticeable. Inasmuch as there are nerve fibers from the parasympathetic sacral outflow, and a few of the ovarian plexus fibers in relation to the main uterine sympathetic supply, these residual symptoms can be easily explained.

The occasional bladder symptoms are very likely due to interference with fibers of the sympathetic and parasympathetic supply to that organ. This may in large part be avoided by guarding against too low an incision of the plexus, i. e., by sectioning only fibers of the superior hypogastric plexus at the lower end, thus sparing the fibers of the hypogastric nerves with their lateral parasympathetic connections. A temporary upset of the bladder nervous mechanism as a result of surgical interference, even when correctly applied, may also be a factor, but the disturbance should be transient.

As stated by Kuntz, the uterine plexus has direct connection with the lower lumbar chain ganglia, lying alongside the lumbar vertebrae. Careful search at the origin of the common iliac arteries will disclose

fine fibers crossing the same. These fibers originate in the lumbar chain and if not severed, may be the cause of residual ache in the distribution of the lower thoracic and upper lumbar spinal nerves.

### CONCLUSIONS

The operation of resection of the superior hypogastric plexus of sympathetic nerves for the relief of dysmenorrhea, rightly belongs in the domain of the gynecologist; one who is able to analyze the individual case and to determine whether everything has been done in a medical way for the relief of the dysmenorrhea. Furthermore, it is necessary that he be able to judge the necessity for removal of gross pathologic conditions if found present. It is not merely a question of whether the surgeon is able to resect the plexus, but whether the individual case has been fairly studied and that nothing remains to afford relief except surgery. In the light of previous radical treatment, such as radiation, hysterectomy, or the use of opiates, the operation here discussed is a conservative one, but the ever present possibility of a mortality must be kept in mind and the operation advised only in those cases in which there is definite evidence that no treatment other than the previously mentioned radical procedures, is of avail. Furthermore, the operator's experience should be such, that in cases of secondary dysmenorrhea requiring other surgery, the operation will be performed with such rapidity as will allow enough time for the added nerve resection without jeopardizing the patient's chances.

There is no deleterious effect on libido, or future pregnancy, because of resection of the superior hypogastric plexus.

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Young, A. M.: Five Hundred and Nineteen Vogt Bromine Tests of Urine for Pregnancy, J. Lab. & Clin. Med. 19: 153, 1933.

The author, in a series of 519 specimens, has shown that the Vogt bromine test (slightly modified) is far from satisfactory for the diagnosis or exclusion of pregnancy. Positive results were obtained in 63 per cent of pregnancy urines and negative results in only 84 per cent of the nonpregnancy urines. The Vogt test, briefly, is a color test for histamine or histidine with a bromine reagent.

The Aschheim-Zondek and Friedman tests are well known and accurate, yet they require the use of mice or rabbits, are expensive and time-consuming, thus there is a need for a simple chemical test.

W. B. SERBIN.

## PNEUMOCOCCUS PELVIC INFECTION IN ADULTS\*

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**I**NFECTION of the peritoneal cavity by the pneumococcus was brought to the attention of the profession by Bozzolo in 1885. Since that time sporadic reports of such cases have appeared in the literature. The first reports were concerned with the disease in children and the pediatricians soon recognized it as a clinical entity. Most of the published reports, however, are by surgeons whose surgical attack upon these cases afforded opportunities for clinical, bacteriologic, and pathologic study.

These early reports indicated that the condition occurred only in female children. As late as 1925 Gibson<sup>1</sup> stated that the so-called primary type was seen only in young girls. Wolfsohn,<sup>2</sup> however, in that same year reported before the Berliner Medizinische Gesellschaft a few similar cases occurring in males. There also began to appear reports of scattered cases occurring in adult females. A study of these adult cases indicates that a large majority have an especial interest for the gynecologist and obstetrician. This relationship is apparent in the following three cases occurring in my practice:

CASE 1.—Mrs. R. S., aged forty-two years, had always been well; three children, youngest 4 years, miscarriage one and one-half years before present illness. Admitted Dec. 28, 1932. Illness began with sudden onset Dec. 23, 1932, with a chill, rise of temperature and pains in her back and bones. A physician who was called diagnosed "Flu." At this time there was no abdominal pain. She did notice, however, a vaginal discharge, thin, purulent, and odorless. December 24: No improvement in general condition but still no abdominal pain. December 25: Had severe chill and developed cramp-like pains in lower abdomen and back. December 26 to 27: Increase in abdominal pains especially below the umbilicus. Some diarrhea, believed to be due to a cathartic she had taken. Bowel movements painful. On the twenty-seventh, had definite pain in right shoulder. Was admitted to the hospital on the morning of the twenty-eighth acutely ill. Temperature 103° F., pulse 100. Examination on admission showed abdomen to be distended with moderate muscle rigidity. Marked tenderness of lower abdomen especially at the left. Cervix somewhat anterior with painful swelling posteriorly and laterally. Vaginal discharge present. White cell count 26,800, polynuclears 90 per cent. Diagnosis: Beginning pelvic abscess. On the twenty-ninth cervix found pushed high behind the symphysis, due to a marked increase of the mass posteriorly. Immediate colpotomy decided upon. Before opening the vagina swabs were taken from the uterus. Incision behind the cervix evacuated large quantity of odorless, flaked pus. Specimen collected for study. Following this the temperature fell to normal on the

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sixth day, and the patient was discharged on the tenth day following operation. The smears and cultures from the uterus showed pneumococcus Type IV. Verified by mouse inoculation. Pus from abscess showed same organism. Blood culture on January 2 negative.

CASE 2.—Mrs. S. H., aged forty-six, married, five children, youngest six years. Admitted on surgical service March 11, 1933. Patient stated that for the week prior to onset of present illness she had had a "cold." March 10 had a severe chill followed by low abdominal pain more pronounced on left side. Pain also extended to right shoulder. Vomited five times; no diarrhea. On day of admission temperature 103.5° F., pulse 100, leucocytes 24,400, polys 97 per cent. Examination on admission: lungs clear, fauces reddened, abdomen distended. Lower abdomen was painful to pressure with rebound tenderness on left side. Cervix normal position; external os admitted index finger, lateral fornices nothing remarkable; posterior fornix indefinite tender fullness. Cervical smear showed pus cells with variety of organisms (types not specified). The above examination was made and recorded by the same interne who had been on the gynecologic service three months before, when the first case here reported was admitted and studied. This fact makes of interest his recorded impression note: "Pelvic inflammation, acute, and in view of onset following an upper respiratory infection believe that the pelvic infection might well be of the pneumococcus type. Gonococcus to be ruled out."

March 15: Patient had pain in right chest, pleuritic in character and on auscultation an occasional friction rub was heard with somewhat diminished breathing; respirations 22. Temperature ranged lower, fluctuating to 100.5° F., pulse 90. Abdominal symptoms somewhat improved. Patient continued with irregular temperature, highest 100° F. with pulse 80-90 until March 30, 19 days after admission. She was then transferred to gynecologic service as the pelvic mass had developed, pushing the cervix high and somewhat to the left. The fluctuating mass behind the cervix could be felt above the symphysis. Patient taken to operating room at once for a posterior colpotomy. While on the operating table before the colpotomy was done, a sound was introduced into the uterus and a moderate quantity of pus escaped; this was collected on a swab. On opening the culdesac a large amount of thick flocculent, odorless pus was evacuated. A sample of pus from the abscess and the swab from the uterus were sent to the laboratory. From the pus obtained from the uterus a smear showed gram-positive bacilli with the same organism in culture. No streptococci seen. The pus from the abscess yielded gram-positive cocci in pairs producing green color in broth and without hemolysis on blood. Bile solubility definitely positive. Pneumococcus Type IV.

CASE 3.—This case is of especial interest and a search of the literature fails to discover a similar one.

Mrs. J. S., aged thirty-six, the wife of a physician, was first seen by me in January, 1924. At that time she had two children, aged seven years, and eleven months. She had been ill since the birth of the last child. This last labor, occurring Feb. 9, 1923, was normal in every respect. Postpartum temperature was normal for three days, then she felt chilly on several occasions, with temperature of 101° F., pulse 90. Lochia not remarkable. During the night of February 13 she had repeated slight chills and aching of the muscles; the following day temperature was 102° F., pulse 100. That night she complained of nausea and severe abdominal "cramps." The following day she was somewhat more comfortable, with lower temperature, and on eighth day it became normal and remained so until the eleventh day when she went home. Her urine having contained much pus, her symptoms were assumed to be due to pyelitis. Following her return home she developed arthritis,

and a number of abscessed teeth were extracted, with some temporary relief. She had much backache and frequent temperature of 105° to 106° F. Some urinary frequency. On Aug. 23, 1923, she was admitted to the hospital for urologic study. Catheterization of the ureters showed normal discharge of urine, and no pus was found in collected samples from either side. There was pain in lower right quadrant during the six days in the hospital; temperature fluctuated irregularly to 101° F. Pelvic examination at this time was said to be negative.

Her subsequent progress was not satisfactory. Her joint pains persisted and on several occasions she was confined to bed with temperature and pain in lower abdomen. The latter part of January, 1924, eleven months after confinement, pelvic examination by me revealed a tender mass the size of a small grapefruit on the right side; uterus somewhat anterior and pushed to the left. Left adnexa free. A diagnosis of right ovarian abscess at that time was made. As the patient's general condition was not good it was decided to drain the abscess through the vagina and allow her condition to improve before removing the sac. Feb. 7, 1924, a posterior culdesac opening was made but no pus found. The mass was firm and very fixed. Leucocyte count was 10,500, 81 per cent polymorphonuclears. For the following ten days temperature was of septic type; pulse 90-100. On February 26, ten days after the colpotomy, a laparotomy was done. Through a transverse incision a mass the size of a small grapefruit presented on the right side. A small area of the upper portion was free of adhesions but at all other parts it was firmly adherent to intestines and pelvis. The appendix and cecum were involved in the mass. The adhesions to the pelvis were extremely dense. The broad ligament was markedly thickened. The bowel was carefully freed by sharp dissection. The attachments of the mass posteriorly were very thick and in freeing it here a small amount of thick odorless pus escaped. The mass could then be removed. A rubber pelvic drain was placed through the right angle of the incision. The left tube and ovary were normal and free of adhesions. Her convalescence was uneventful and she was discharged on the twenty-third post-operative day and since the operation she has been in the best of health.

The gross pathology here did not conform to the ordinary pelvic infection. The mass consisted of ovary and tube, the ovary composing the greater part of the mass. The pathologist reported numerous abscesses of various sizes throughout the ovarian mass. The tube was much thickened and contained a small amount of pus similar to that in the abscesses of the ovary. Smears from these abscesses showed gram-positive diplococci. Cultures from the various abscesses yielded the same organism in pure culture, all of which answered to the requirements of the pneumococcus. Diagnosis: right salpingitis and multiple ovarian abscesses of pneumococcus origin.

It is somewhat difficult in this case to reconstruct the course of events leading to the final pathology. The onset three days post-partum was suggestive of a pneumococcus pelvic infection. The initial chill followed by a rise in temperature and symptoms of general systemic infection, which in turn were followed two days later by further chills with severe "crampy" pains in lower abdomen, was in every way characteristic. The fact that these symptoms subsided in a few days may be accounted for by a pneumococcus of low virulence becoming confined to the tube, with later involvement of the ovary. The attacks of pain and temperature on several occasions during the succeeding months may have indicated a new abscess in the ovarian mass until finally the pathology found at operation had developed.

Certainly urologic examination during the time when these attacks were occurring, yielded no evidence to justify regarding such attacks as due to a pyelitis. Finally, removal of the mass resulted in prompt and complete recovery.

The literature yields cases comparable to these here reported. Wolfsohn reports a case of a thirty-seven-year-old woman, ill fourteen days; large collection of pus below the umbilicus evacuated. Postoperative pneumonia; recovery. Also a woman of twenty-eight years who on the day following an abortion was taken suddenly ill with abdominal pain and a rise in temperature. A large culdesac collection was later evacuated with prompt recovery. Pneumococcus found. Gibson reports a case of an unmarried woman twenty-five years old who had been ill for three weeks with "cold" and mild abdominal symptoms. Acute onset with chilly feelings, cramps, diarrhea, and vomiting. Median laparotomy yielded the characteristic pus confined to the lower abdomen. Culture of pus from the nose and throat showed pneumococcus Type I. Cultures from vagina and cervix were negative. In a discussion of Gibson's paper, C. H. Peck, New York, reported the case of a woman thirty-two years old who had been operated upon for mastoiditis. Five days later a large right-sided abdominal abscess developed and was opened. Pneumococcus, Type III, was found in the pus of the abscess and in the mastoid. Death followed.

A review of the reported cases also suggests that the pneumococcus may be the sole causative agent in infections following abortion or labor, occurring either as a very early acute puerperal process or as one appearing several weeks postpartum. One patient in Wolfsohn's series developed an infection twenty-four hours after an abortion. Baetjer<sup>3</sup> reports a woman twenty-seven years old who five weeks after normal labor and uncomplicated puerperium, was suddenly seized with acute pelvic pain with the rapid development of a generalized pneumococcus peritonitis which resulted in death. At autopsy the left tube was apparently the focus.

The second case of Baetjer's was a woman aged twenty-five, who six weeks after a normal labor and puerperium, was seized suddenly by severe pain in the lower abdomen. There had been no preceding indications of upper respiratory infection. Blood culture was negative. Laparotomy evacuated a thin, turbid, purulent fluid. Culture was a pure growth of the pneumococcus, Type II. Two days later pleurisy and a lobar pneumonia developed, followed by an abscess of an upper lobe which finally ruptured, and recovery resulted. At the time of the pneumonia, the blood culture was positive. Baetjer records a low leucocyte count in his two cases.

Two cases reported by McCord<sup>4</sup> occurring in the early puerperium are of interest. The first patient was a negress, eighteen years of age. On the third day following a spontaneous labor she was seized with a severe pain in the lower abdomen. She had a slight chill and a rise of temperature to 103.2° F. with a pulse of 128. This case progressed rapidly to the picture of general peritonitis. The abdomen was opened under novocaine and a large amount of pus was drained. The patient died four days after onset of illness. The blood culture and smears both at operation and autopsy were positive for the pneumococcus.

His second case was also a negress, aged eighteen, admitted in labor. She was delivered spontaneously and returned to the ward with normal temperature, pulse, and respiration. Twelve hours later she complained of being cold and of pain in the abdomen. Her temperature was 103.2° F., pulse 108. She died four days later. Autopsy showed a general peritonitis and endometritis with involvement of tubes and ovaries. The blood culture was reported as pneumococci. In neither of McCord's cases had a vaginal examination been made.

A somewhat similar case is reported by Seymour.<sup>5</sup> A woman of twenty-four was delivered by low forceps. Seven days postpartum, she had a chill and temperature

rise to 103° F. The following day the uterus was swabbed out and smears showed a gram-positive diplococcus. Peritonitis developed rapidly. Abdomen was opened with the evacuation of two pints of turbid fluid. Drainage of the pelvis and abdomen resulted in eventual recovery. The pus yielded a pure growth of pneumococcus.

The French literature yields two cases. The first is that of Apert.<sup>6</sup> A young primipara with a marked coryza and a profuse serious nasal discharge, was delivered normally of twins. The day following delivery there was a sudden rise of temperature and abdominal distention. The following day there was profuse diarrhea with continued fever. Fluid was diagnosed "at the base of peritoneal cavity." (In culdesac?) A small low median incision was made and a serofibrinous, somewhat purulent, fluid escaped. Examination showed it to be pure pneumococcus. A suppurative otitis developed and pus from both nose and ear also showed the pneumococcus.

Darrèr and two collaborators report a woman twenty-six years old who had had a normal confinement. Three weeks postpartum she was confined to bed for a few days with a pain in the right iliac fossa accompanied by some diarrhea and a yellowish leucorrhea. She had apparently been well but five days later a similar attack occurred. Two months postpartum she was seized one morning with acute abdominal pain, vomiting, and profuse diarrhea. She was admitted to the hospital on the same day. Twenty-four hours later she had violent abdominal "cramps." Examination showed pouch of Douglas painful but no masses were recognized. Low median laparotomy was done with evacuation of yellowish, odorless, fibrinous pus from the pelvis. Pelvic drainage; final recovery. Pus showed pneumococcus.

A review of these and other cases makes it reasonable to divide pneumococcus pelvic infections in adult females into four groups:

I. The pelvic abscess in which the infection, having become walled off early, remains confined to the pelvis.

II. The generalized peritonitis in which the entire abdominal peritoneum becomes the abscess sac.

III. An infection confined to the tube and ovary. (Third case reported by writer.)

IV. Puerperal infection following either abortion or labor at term. Such infections may occur early in the puerperium, or during the later weeks of involution. Obviously such an infection at that time may develop into a condition to be classified under one or another of the above groups.

The recognition of these four groups has a practical bearing on the diagnosis, prognosis, and treatment.

Those who have written on the subject have discussed the etiology thoroughly. The review of reported cases indicates that on clinical evidence the majority have their origin in the genital tract. The fact, however, that pneumococcus peritonitis may occur in males, both children and adults, as proved by reports of a number of observers, points to other possible avenues of invasion. The blood stream, lymphatics, and intestinal tract have been discussed. If the infection in males finds its way to the peritoneum by one of these latter channels, it is logical to assume that at least a small proportion of cases in females may also occur in the same way. We are justified in assuming,



however, that a very large proportion of these infections in females do reach the peritoneum by the genital tract.

Michant<sup>8</sup> in 1901 suggested classifying cases of pneumococcus peritonitis into primary and secondary, and this classification generally has been followed. I believe, with some others, that this classification should, for a better understanding of the condition, in adults at least, be abandoned. Pneumococcus peritonitis is a comparatively rare complication of pneumonia and in some reported cases pneumonia has followed, instead of preceded, the invasion of the peritoneum. To adhere to this classification ignores the less obvious focal points from which an infection may spread. A number of cases reported in adults do give a definite history of an upper respiratory infection which antedated or was coincident with the pelvic infection. My first patient was ill several days with what was considered the "flu." The second had a definite upper respiratory infection.

If in the future more careful inquiry is made, I believe that a considerable number of these cases will reveal evidence of such infections. Granting the possibility that these conditions do play a rôle in the pelvic infection, there arise some pertinent questions. Are the latent pneumococci harbored in the nose and throat of many normal persons, activated by the bacteria of the "common cold," making it possible for them to invade the blood stream? Or are these foci the source of an infection that is carried directly to the genital tract? McCartney<sup>9</sup> has argued convincingly for direct invasion of the genital tract in children. He produced the disease in a monkey by that means. It is much easier to accept this view in the case of children than it is in adults. If, however, these pneumococcus vaginal infections in children invade the uterus and pelvis so readily, these bacteria possess a tendency to spread on their mucous surfaces that the gonococcus does not, as gonorrheal pelvic infection in children is extremely rare.

If it be a blood stream infection, it must be assumed that it reaches the uterus or tubes and produces an endometritis or salpingitis in much the same way as the tubercle bacillus, for all other infections of the pelvis are due to direct invasion of the canal. Unfortunately for the blood stream theory, animal experimentation has added nothing to its support, and clinically, a positive blood culture is not always found. So far as adults are concerned it must be admitted that there is at present no evidence that satisfactorily accounts for all cases of pneumococcus pelvic infections.

The clinical manifestations of the disease in adult females are quite constant and characteristic. The outstanding features are:

1. There is often a previous indisposition usually associated with the symptoms of an upper respiratory infection. When a pneumococcus pelvic infection is suspected, careful inquiry on this point should *always* be made.

2. The invasion of the peritoneum is characterized by its sudden onset. There are chills or "chilly feelings." The pain is sudden, severe, and located in lower abdomen. The patient often describes it as "crampy" in character. This may be accounted for by the fibrinous exudate that the pneumococcus so promptly calls forth and the effect of peristalsis upon these surfaces. Further distribution of the pain will depend upon the spread of the process. Nausea or vomiting is present in a large proportion of cases, either at the onset or later. In contradistinction to peritonitis from other causes, diarrhea is not uncommon. The temperature may rise to  $103^{\circ}$  or more following the chill. The pulse rate at first is high, but with early localization, the rate drops out of ratio with the temperature, which may remain high. A high leucocyte count early of 20,000 or more is usual with a polynuclear count of 90 per cent or higher.

Invasion of the blood stream may or may not take place. Blood cultures, if positive, may be found early or at any stage of the disease. The presence of the pneumococcus in the vaginal discharge is like the positive blood culture, an uncertain quantity. Positive vaginal smears have been recorded in about 50 per cent of cases in children. Adult cases have not been carefully enough studied to make observations on this point of value.

It is not to be expected that the physical signs associated with a pneumococcus pelvic infection in adults will differ essentially from similar pelvic infections from other causes. Of much importance is the early tenderness, and the sensation of fullness in the culdesac imparted to the examining finger. The pneumococcus on a serous surface promptly calls forth a fibrinous exudate and in addition it is a rapid pus producer. This may account for these early pelvic findings. With localization, the culdesac collection will usually develop very rapidly or, less commonly, it may require a number of days before the abscess markedly displaces the cervix.

With a fulminating spread the evidences of general peritonitis are, of course, present. The one distinguishing point, however, is the rapid formation of pus which takes place earlier and in far greater quantity than in peritonitis from appendicitis or other causes. It should be possible to determine early the presence of this fluid. Some observers have noted that the abdominal wall is less tense than in other forms of peritonitis and that later it may even have a somewhat doughy feel. The amount and character of pus may account for this.

It is not surprising that a preoperative diagnosis has very rarely been made. The second case here reported was diagnosed by the interne upon the history, the physical findings and the fact that he had become pneumococcus conscious. The first essential for the diagnosis of any pathologic condition is that the clinician shall have in mind the possibility of its occurrence. These patients have been mis-

taken and operated upon for various abdominal conditions, or the abdomen has been simply drained on general surgical principles. In practically all of the reported cases the diagnosis has only been made postoperatively by the bacteriologic findings. The surgeon, however, who has seen the characteristic odorless, flocculent pus of these cases, should, in the majority of instances, be able to make a table diagnosis. This in itself is important as it forestalls a futile search for an abdominal focus and enables the surgeon to confine his attention to establishing adequate drainage. Undoubtedly, with the condition in mind and with due regard to the history and clinical features, these cases in the future will be more frequently diagnosed.

As to prognosis, in reviewing the adult cases, two facts stand out prominently. Patients belonging to Group I recover promptly on draining the abscess by posterior colpotomy. Low abdominal drainage of this group, as was done in some cases, seems not to be followed by equally good results. In contrast to these results in Group I, the cases of generalized peritoneal infection of Group II have a high mortality. This is especially true of those cases that occur early postpartum. Other factors such as the virulence of the organism, and complications, play the same rôle in the prognosis as in all other infections.

It would seem somewhat premature at this time to discuss at length the treatment of these patients. The treatment of the patients in Group I is simple and satisfactory. The treatment of the patients in Group II by drainage has not been promising. It would appear at present that until the clinical and laboratory features have been more carefully elaborated with a view to determine better the criteria upon which an early diagnosis may be made, there is little hope of improvement in the present mortality of this group. If there comes a time when it is possible, on the evidence, to drain the culdesac early, it is not unreasonable to expect that such prompt drainage would result in the infection remaining localized in the pelvis and that in fewer cases would it spread to the general peritoneum. Colpotomy is such a simple and safe operative procedure that there is little that can be urged against it.

In the presence of a well-developed general peritonitis adequate drainage is the only hope. In such a case it would seem that a median pelvic drain with bilateral flank drainage would meet the indications best.

#### CONCLUSIONS

1. Pneumococcus peritoneal infections in the adult female are of more frequent occurrence than published reports would indicate.
2. They have an especial interest for the gynecologist and obstetrician.

3. The genital tract is the most frequent path of infection, but a small percentage probably occurs by other means.

4. More careful histologic and bacteriologic autopsy studies of the pelvic organs should be made when opportunity presents.

5. The disease in adults should, because of the clinical features peculiar to them, be studied apart from the disease as seen in children.

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1255 DELAWARE AVENUE

## INTRAUTERINE APPLICATION OF CARBON IN INCOMPLETE ABORTION\*

B. H. CARROLL, M.D., TOLEDO, OHIO

AT PRESENT the accepted treatment of abortion is along the well-established conservative lines. Instrumentation in which the uterine cavity is entered, cervical or vaginal packs, even examination except under sterile conditions, are, generally speaking, contraindicated. However, it may be necessary to remove the uterine contents. In the presence of infection this operative procedure carries a very definite risk to the mother. The cause of death in nearly every case is directly or indirectly due to infection. Attempts to safeguard this procedure by the use of local antiseptics have not been successful. The uterine cavity cannot be made sterile except for very short periods of time.

During the war, German research workers revealed that carbon produced at a low temperature had a much greater power of adsorption than the average carbon made without careful thermal control. This carbon is known as activated carbon and has from thirty to three hundred times the power of adsorption possessed by ordinary carbon. The highest grade is 99.9 per cent pure. Consequently it is very porous and easily pulverized into the finest powder. A comparatively

\*Read at the Forty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 6, 7, and 8, 1934.

of less than  $100.2^{\circ}$  and are considered, for this report, as afebrile. As might be expected, a large percentage of the whole group had a primary or a secondary anemia. Half of the patients had a hemoglobin of 60 per cent or less, one-third were below 50 per cent, 7 patients were below 30 per cent.

With each patient the uterus was emptied and carbon inserted as promptly as possible after the diagnosis was made, usually within twenty-four to forty-eight hours.

In this group there were no deaths. Ten patients of this series remained in the hospital more than seven days. Two were held for further transfusions and general building up. Eight patients continued to run a temperature over a period of several days. One of these had a severe pyelitis on admission, which was probably the exciting cause of the abortion. A second patient with active tuberculosis had a therapeutic abortion in which carbon was inserted; two months later a dilatation and curettage was done because of uterine bleeding. A piece of placenta was recovered and carbon was inserted. This patient promptly developed a parametritis. A third patient had a well-established parametritis on admission to the hospital and was about bled out. After removing tissue which was protruding from the cervix, carbon was inserted to control the hemorrhage. This patient had a stormy convalescence, forty-six days in the hospital. Five other patients developed a parametritis after using the carbon. Whether this complication was due to the already infected abortion or occurred in spite of our procedure, I am not prepared to say. This is a morbidity rate of 8.8 per cent for the infected cases and 5.6 per cent morbidity rate for the whole group.

The average time of all patients in the hospital was seven days after operation, a saving of 25 per cent in hospital days when compared with conservative treatment. After dismissal from the hospital no unfavorable symptoms were reported. Occasionally small flecks of carbon would be recovered from the vagina two weeks after operation, but this caused no distress. The menstrual cycle was reestablished as usual. Seven of these patients have since become pregnant. Three were delivered of normal babies, two induced abortion upon themselves and are included in the series a second time. The terminations of the other two are unknown.

For obvious reasons, it is difficult to check by laboratory tests the contention of the foreign workers, as enumerated earlier in this paper.

Carbon changes the pH concentration of a culture medium toward the acid as is shown in Table I. This increased acidity affects the rapidity of growth and staining characteristics of the streptococci.

TABLE I

Br. Br. Culture		Before incubation pH 8.0
Br. Br. Culture		24 hr. incubation pH 7.4
Br. Br. Culture	plus carbon	24 hr. incubation pH 6.8
Br. Br. Culture (pH 0.8) plus Strep.		24 hr. incubation pH 6.6
Br. Br. Culture (pH 0.8) plus Strep.	plus carbon	24 hr. incubation pH 6.2
Br. Br. Culture (pH 0.8) plus Strep.		48 hr. incubation pH 6.4
Br. Br. Culture (pH 0.8) plus Strep.	plus carbon	48 hr. incubation pH 6.0
Br. Br. Culture (pH 0.8) plus Staph.		24 hr. incubation pH 6.4
Br. Br. Culture (pH 0.8) plus Staph.	plus carbon	24 hr. incubation pH 6.0

is definitely changed and this may influence the life and virulency of the organisms. Also the marked absorptive power of carbon causes a local hyperemia and increases the patient's resistance to infection. Some authors feel that there is a direct mechanical stimulation of the reticuloendothelial system to a phagocytosis by the carbon. It has been shown that carbon changes the pH concentration of a medium to the acid side, and this has a pernicious influence on streptococci. Acting as a foreign body in the uterine cavity, it stimulates contraction of the muscle. Small particles of carbon dust promote rapid thrombus formation in the mouth of vessels.

Clinical results reported included a sudden fall of temperature in febrile cases with no recurrence of fever; the afebrile patient remained afebrile; there was immediate cessation of hemorrhage; lochia containing carbon lasted from three to five days. There was a marked improvement in the general condition of the patient, and prompt deodorization. The hospital days were reduced from twelve to ten, and fewer complications and no injurious effects were noted.

In our early experience in using carbon the results were not as encouraging as we had hoped for, although the patients were less toxic and temperatures lower; the fever persisted in some patients and several had hemorrhage.

These patients were in the third and fourth month of their pregnancy, at which time the placenta has developed to a considerable size and has characteristic qualities. We know that bacterial growth is most prolific on devitalized tissue and that the hemorrhage usually comes from the placental site. It seemed plausible to us that by removing the placenta and products of conception first, then the action of the carbon would not be handicapped or overwhelmed by a mass of decomposing tissue. Proceeding on this theory, our patients were first given a physical examination and a definite diagnosis of incomplete abortion or abortion in progress was made. We tried to diagnose other pelvic pathology, especially extension of infection beyond the uterine cavity. If our findings were negative we proceeded along the usual lines to empty the uterus. It was necessary to dilate the cervix in about half of the cases, placental or ring forceps being used to grasp the retained tissues. Occasionally it was necessary to use a dull curette. Care was used to traumatize the normal tissue as little as possible, in the operation. After emptying the uterus the cavity was carefully filled with carbon pencils.\* Almost immediately a frothy black mixture exuded from the cervical os, which is the lochia of the succeeding few days. Five of our patients continued to have hemorrhage so that it was necessary to put in a light gauze pack.

The patient was then returned to bed and given general nursing care. We felt that with a clean uterus and the carbon acting as a foreign body to stimulate contraction, no specific medication was indicated. Consequently, we deviated from the German procedure and did not use ergot, pituitrin, or any of their derivatives. A few patients were given transfusions.

Following this type of treatment, we have the records of 106 consecutive cases of abortion in which carbon has been used in the uterine cavity. The length of time the abortion had been in progress varied from two months down to the therapeutic abortion. On the day preceding or the day of the operation sixty-eight patients carried a temperature of 100.2° or above. Thirty-eight patients had a temperature

\*Imported by Merck & Co., Rahway, New Jersey.

of less than 100.2° and are considered, for this report, as afebrile. As might be expected, a large percentage of the whole group had a primary or a secondary anemia. Half of the patients had a hemoglobin of 60 per cent or less, one-third were below 50 per cent, 7 patients were below 30 per cent.

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Br. Br. Culture (pH 0.8) plus Staph.		24 hr. incubation	pH 6.4
Br. Br. Culture (pH 0.8) plus Staph.	plus carbon	24 hr. incubation	pH 6.0

Gram stain smear from Br. Br. culture plus streptococcus plus carbon after twenty-four hours' incubation show a few organisms, which take a negative stain.

Subculture made on fresh Br. Br. culture shows a growth of streptococcus at the end of twenty-four hours.

Gram stain smear from Br. Br. culture plus staphylococcus plus carbon twenty-four hours' incubation, no organisms found.

Subculture made on agar slant shows slight growth of staphylococcus.

This increase of acidity may well take place in the uterine cavity inhibiting or interfering with bacterial growth.

There were no postoperative hemorrhages in those cases in which all of the material was removed. Carbon acting as a foreign body, probably, helps to keep the uterus contracted and also hastens coagulation.

### CONCLUSIONS

This is a relatively small number of cases from which to draw anything but general conclusions. It does seem that the patients are not endangered by the carbon per se; that symptoms of toxemia were promptly relieved. There was a 25 per cent shorter convalescence. There were only six patients in whom the infection extended into the parametrial tissues after the use of carbon. There were no deaths.

These results, which are in close accord with those already published, should warrant further investigation as to the advisability of treating incomplete abortions, whether infected or not, with activated carbon.

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A seventeen-year-old girl entered the obstetric service under the impression she was pregnant and was subsequently found to have a large solid ovarian tumor weighing 5,300 grams. The tumor fell into the group designated by Robert Meyer as disgerminoma. The right ovary appeared to be normal and was not removed. There had been no disturbance of menstrual or sex functions, but there was a mild grade of malnutrition, infantilism and hypogenitalismus.

Disgerminomas are tumors arising from an undifferentiated germinal epithelium of the gonad, and do not possess any hormonal function. They have previously been described as large cell alveolar sarcoma, endothelioma, lymphangioendothelioma, granulosa cell tumor and chorioectodermal epithelioma.

WILLIAM F. MENGERT.



# MONOAMNIOTIC TWIN PREGNANCY\*

## A CASE RECORD WITH REVIEW OF THE LITERATURE

JAMES K. QUIGLEY, M.D., F.A.C.S., ROCHESTER, N. Y.

**I**NCIDENCE.—The rarity of monoamniotic twin pregnancy is sufficient reason for this case report. J. W. Williams<sup>110</sup> in a brief reference to this condition said that there were 44 cases in the literature, those of Holzapfel's series. DeLee in the 1928 edition of his Textbook said 40 cases had up to that time been reported. However, one year prior to Holzapfel's<sup>51</sup> monograph or in 1903, Alfieri<sup>5</sup> had collected and described in detail 71 cases. These monographs together with that of Ahlfeld<sup>4</sup> remain the best contributions to the study of this interesting and unusual condition.

There are but eight references with case reports in the American literature, from that of Reynolds<sup>87</sup> in 1835 to T. J. Williams in 1931—only one case in the last twelve years. In none of these articles is there a thorough review of the literature and the case here reported is the only full-term pregnancy and the only instance of a surviving child in the American literature.

Resinelli<sup>88</sup> estimates that monoamniotic twin pregnancy represents 2.11 per 100 cases of uniovular twins. Alfieri found six monoamniotic out of 1,535 twin pregnancies; Ahlfeld in 506 twin pregnancies found 60 monochorionic and three monoamniotic. It would seem that Müller's estimate of one per 6,000 births is too great an incidence, for this would mean one monoamniotic for every 70 cases of twins and the paucity of cases in the literature does not warrant such an estimate. Contrasted with Müller's<sup>72</sup> estimate of one per 6,000 is that of Rosenberg of one to 60,000 births.

Dietrich<sup>27</sup> said, "It is given no obstetrician to see more than one case in his experience." That is not quite true, for Schultz,<sup>97</sup> Spaeth,<sup>105</sup> Th. Wenzel,<sup>116</sup> Wolf,<sup>122</sup> and Pallin<sup>80</sup> have published descriptions of two cases each. Every author writing upon the subject of monoamniotic twin pregnancy has emphasized its extreme rarity.

Jeannin<sup>54</sup> says that in a triple pregnancy two of the fetuses may be contained in one amnion. I found eight such cases reported. Ausch<sup>6</sup> and Hauser<sup>43</sup> have seen in two cases of quadruple pregnancy, three of the fetuses enveloped by one amnion and lastly, Caseaux cites a case of monoamniotic quintuple pregnancy delivered in Pigné.

In the recent well-known case of Dr. DaFoe<sup>25</sup> in Canada of quintuplets there was one placenta and five amniotic sacs.

\*Read at the Forty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, White Sulphur Springs, W. Va., September 6, 7, and 8, 1934.

NOTE: For lack of space the tabulation of cases could not be included here, but may be found in the current Volume of the Association's Transactions.

## CASE REPORT

Mrs. C. O'K., para i, aged thirty-four, married three and one-half years; last menstrual period, Jan. 29, 1933, quickening June 12. Expected date of delivery, Nov. 5, 1933. Twins were diagnosed September 29 and aside from discomfort from tremendous distention (height of fundus on November 9 was 45 cm.), the course of her pregnancy was uneventful. Only one fetal heart was heard at her numerous prenatal visits and that was in the right flank. One vertex descended into the pelvis a month before delivery. Because of extreme discomfort and the fact that the patient was a few days past her estimated date, labor was induced by castor-oil and quinine on November 10.

The labor was short for a primipara, eight hours and thirty-seven minutes. The amniotic fluid was meconium colored on rupture of the membranes and naturally it was thought that the first child might be in danger. This child was delivered

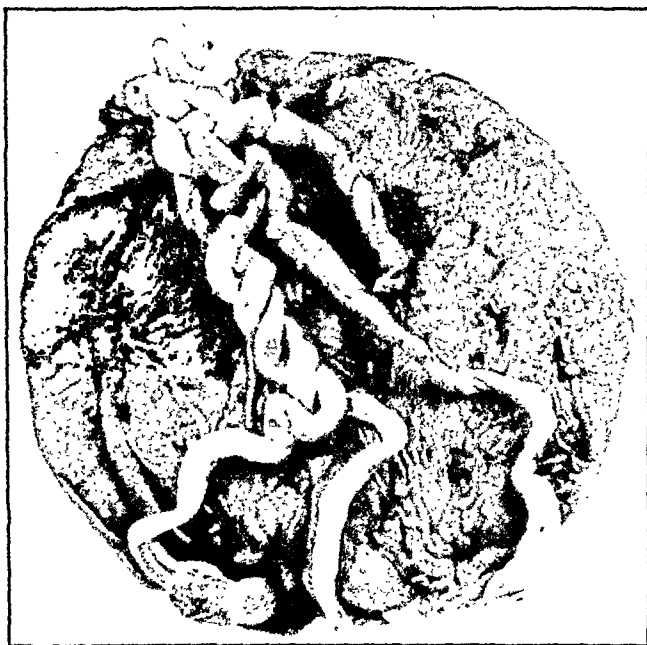


Fig. 1.—Fetal surface of the placenta showing knot formation and twisting of the cords and their marginal insertion.

L.O.A. spontaneously and was in good condition. The second child in R.O.P. position was delivered by an easy Scanzoni maneuver. It was born in pallid asphyxia, the heart action was feeble and 40 to the minute. All known methods of resuscitation were employed, such as tracheal catheter, the administration of  $\text{CO}_2\text{-O}_2$  mixture, Alpha lobelin injection and adrenalin injected into the heart which continued to beat for twenty-five minutes, but respiration was never established. The twins were females and weighed, first twin (survived) 2,975 gm., second twin 3,114 gm.

The cause of the asphyxia was discovered on the delivery of the placenta which measured  $29 \times 23$  cm. and weighed 1,545 gm. There was only one amniotic sac, the cords were inserted marginally, 9 cm. apart; the insertion was almost velamentous; there was no anastomosis. There was no indication of a partition remnant. The cord of the second baby was entwined with that of the first and tied into an indescribable mass of knots, almost the size of a man's fist. The cord of the first baby passed through this mass but was not involved in it.

## HISTORY

Hippocrates mentioned mono chorionic twins but said nothing as to both being enclosed in one amnion. Mariceau, Levret and Bandelocque denied its existence. Jeannin<sup>54</sup> and Eleuterescu<sup>32</sup> of France both credit Viardel, a fellow countryman, with the first description of this condition in 1671, Alfieri, however, contradicts this and says that in 1612 Bocalini and in 1,649 Jakob von Back<sup>7</sup> demonstrated that twins might both lie in the same amnion. Thus three or four descriptions appeared in the seventeenth century, only one in the eighteenth and beginning with Tiedeman's<sup>110</sup> case in 1805, there were up to 1903, 71 cases collected by Alfieri. In 1904, Holzapfel collected 39 already reported by Alfieri and three, including his own, not in Alfieri's collection. I found eight cases reported prior to the monographs of Alfieri and Holzapfel but not included by either and I have collected 30 additional cases reported since 1904. These together with the one here reported totals 113 cases. However, included in Alfieri's series were four credited to Weiss, cited by

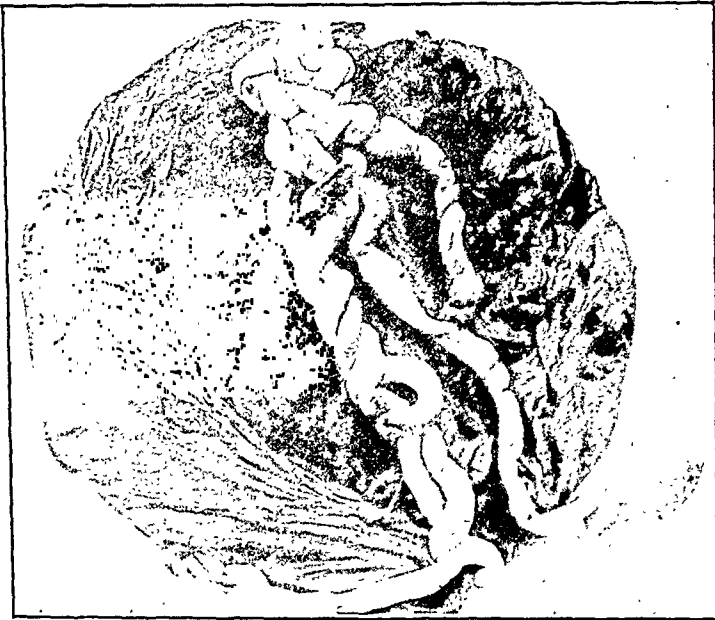


Fig. 2.—Maternal surface of the placenta.

Hink.<sup>40</sup> Both Alfieri and Hink doubt, because of the rarity of the condition, that one man had observed as many cases. Allowing for this discrepancy then, it might be said that to date, 109 cases have appeared in the literature.

## ETIOLOGY

There are two theories as to the origin of monoamniotic twin pregnancy. The first, or primitive duality, in which there are originally two amnions, the partition between the two sacs is broken down early in fetal life; the second, that of primitive unity, in which case there is one amnion from the beginning. Two blastodermic vesicles meet and join and are enveloped by one amnion.

There are many supporters for both theories. Kleinwachter,<sup>60</sup> Leishman and Ahlfeld believe in the first, that there are originally two amnions and that the partition between disappears. How this comes about is a matter of conjecture. Kleinwachter holds that due to movements of the fetuses, a tear occurs and the remainder atrophies. Ahlfeld thinks the pulsation of the two close lying cords causes a lacera-

tion through friction. Holzapfel agrees with this. In favor of primitive duality is the presence of a reste or remnant of the partition, between the cord insertions on the placenta. Ahlfeld, Holzapfel and Podzurodsky<sup>20</sup> have minutely described such remnants and a number of other observers mention their presence, while in more than a dozen cases it was distinctly stated there was no partition reste found.

Schultze and Bumm<sup>21</sup> are proponents of the primitive unity theory. They argue that if we are to believe in the tearing of a partition between two separate amnions, it would occur in biovular pregnancies as well. Some of the cases have shown a common cord for both fetuses, blended or anastomosed; this, of course, is in favor of the primitive unity idea.

Bifurcated cords were present in five of this series and in many, the cord insertions were very close together, this arguing against primitive duality.

It is conceivable in view of the evidence on both sides, that both schools may be right, that in some cases there are two amnions from the beginning and in others,

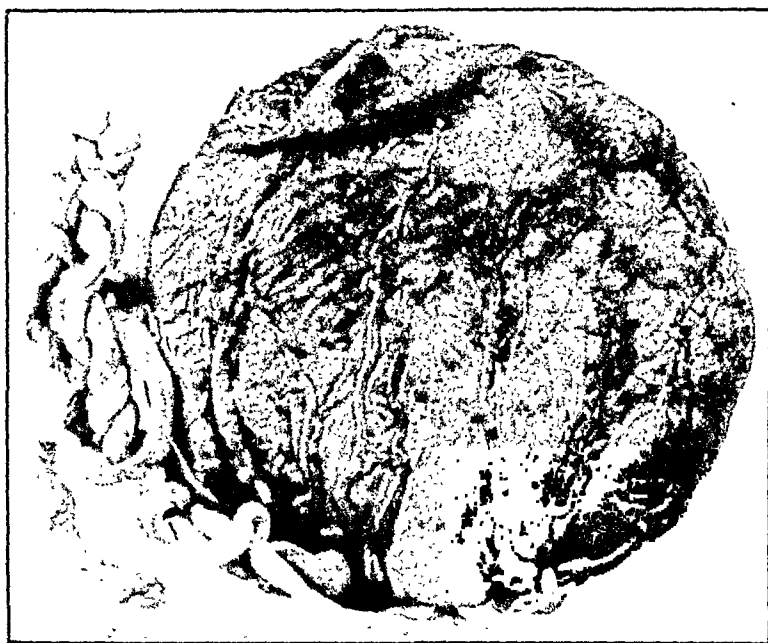


Fig. 3.—Fetal surface of the placenta showing absence of an amniotic partition.

there is but one. One of the many interesting conjectures presented in twin pregnancy is that of the origin of double monsters.

O'Schultze, quoted by H. H. Wilder<sup>117</sup> grouped the types of twinning in man under four categories:

1. Two separate blastodermic vesicles with two deciduae reflexae and two placentas; this case is probably one in which there are two separate eggs, either from the same or opposite oviducts and implanted at some little distance from each other.

2. Two separate blastodermic vesicles inclosed in a single decidua, placentas fused with one another but with separate sets of umbilical vessels; this case is more frequent than (1) but apparently results from the same general cause, i.e., two separate eggs which are, however, implanted nearer together.

3. Two amnions and two umbilical cords with a single placenta, in the middle of which the two cords meet and upon which the umbilical vessels closely anastomose. These are inclosed in a single chorion and covered with a single decidua reflexa. The twins are always of the same sex.

4. Similar to (3) but with both embryos inclosed in a single amnion. *This is a very rare case*, explicable only by postulating a single blastodermic vesicle upon which the two embryonal areas are nearly or entirely in contact with one another. In such a case there would be an almost irresistible tendency toward the fusion of the two embryos, along the line of mutual contact, thus producing some form of composite monster.

The close connection of (3) and (4) suggests that many cases of compound monsters come under the same category as separate duplicates. This is quite probable but such forms arising from a secondary fusion would be more asymmetrical and more or less unequal and would come under the class of antosite and parasite rather than that of symmetrical or genuine double monsters.

Conjoined twins and double monsters are divided into two types, one in which the components or compound parts are equal to and the symmetrical equivalents of one another, Diplopagi, the Siamese type; the other, unequal and asymmetrical monsters, one component of which is smaller and dependent upon the other, antosite and parasite, sometimes the parasite is merely a head or head and arms attached to the antosite at or near the epigastrium or upper part of the abdomen.

There was in this collected series no true case of diplopagi found, which would argue against the condition of a single amnion in twin pregnancy as a cause for fusion to produce symmetrical monsters or diplopagi. However, Fischer<sup>34</sup> in 1866 advanced the theory that double monsters are the result of an early total fission of the embryo, followed by a secondary fusion of the parts. Wilder is inclined to endorse Fischer's theory. He says, "It will be remembered that in the account of intrauterine relations of duplicate twins, a condition was described in which the twins were not only monochorial but monoamniotic. This appears to me to present many possibilities for fusions."

Twinning carries with it hazards for one or both of the fetuses and the commonest cause is due to anomalous fetal circulation. Frederick Schatz<sup>35</sup> has probably written more upon the development of one-egg twins than any other observer. His material was extensive and his researches were published in the *Archiv für Gynäkologie* between the year 1882 and 1900. He says, as the result of an anatomical derangement or asymmetry of the vascular system, one of the twins is robbed of the blood supply necessary for its normal nourishment and functioning. The result is a progressive weakening of the heart with an accompanying decrease in size. The pressure of the blood from the strong opposite twin comes to bear upon this weakened heart and if sufficiently strong, overwhelms it and brings its rhythm to a standstill. This heart later atrophies. Life is maintained by the opposite or injured twin through what Schatz calls the third circulation, an anastomosis between the vessels of the respective twins in the placenta. Alfieri found in his collected series, several acardiac parasites and I found an additional one.

#### CLINICAL SIGNIFICANCE

The clinical significance concerns chiefly the fetuses for in all the cases reported, the delivery has not been more difficult than in any case of twin labor.

One might suppose that collision of the twins, that is, the simultaneous engagement of two presentations might complicate the delivery but in the cases already reported this has not happened.

Holzapfel says, "I consider it probable that by a collision of the twins, the partition is made to disappear." Here he refers to very early pregnancy. This pre-

supposes some opening in the amniotic partition *de novo*, through which collision might cause further tears and a disappearance of the remainder of the wall between the sacs. This does not sound plausible to the writer. Of the 109 cases here reviewed the period of gestation reached was as follows: full term 26, premature but viable (six and one-half to nine months) 25, nonviable 24, and not stated 34.

The chief clinical interest is the danger of death of one or both of the fetuses from twisting or knotting of the cords, which is very common.

In Roberg's<sup>80</sup> collected series there were 25 cases of twists and knots. Piltz<sup>83</sup> found 28 cases. In my review of 109 cases so far reported, torsion or true knot formation was reported 58 times or 53.2 per cent. In many of these the knots were multiple and so complicated that the knots could not be counted. Not only has this resulted in the death of one or both twins at or near full term but some of the early abortions were undoubtedly caused by this disturbance in the fetal circulation. The danger at delivery often arises from traction on the cord of the first twin, tightening the knots in the cord of the second, as in the case here reported, the cord of the first twin passing through many knots of the second. Bihler<sup>14</sup> called attention to this danger to the second twin.

Dietrich's<sup>82</sup> experience and that of Hammerschlag<sup>45</sup> was practically identical with mine, that is, the cord of the second twin was caught in a knot of the first and the circulation cut off by the descent of the first twin. In the case reported by Newman<sup>73</sup> the midwife pulled upon the first cord, causing compression of the second. Podzahrodsky<sup>86</sup> relates an interesting complication where the midwife cut a cord tight about the neck of the first twin. It proved to be the cord of the second twin and only by a prompt delivery effected by Podzahrodsky were both twins saved.

Burger<sup>10</sup> says, "For one or other of the children during the intrauterine life, no danger from twisting of the cords is likely to occur. Indeed, one found in each of the described cases, cord furrows on the umbilical cords." These are interpreted, according to Tarnier and Schauta and A. Martin as a postmortem change, "so that the danger of compression during uterine life does not seem to be great." This conclusion does not seem reasonable in view of the fact that abortion occurred in this series 15 times in which there was knotting or twisting. As proof against knotting and twisting of the cords is the length of the cords and the freedom of movement born alive with knotted and twisted cords. The only explanation to be advanced for knotting and twisting of the cords is the length of the cords and the freedom of movement afforded by the presence of two fetuses in one sac. Sammlhammer<sup>80</sup> thought the twists came from shaking of the mother during a journey over a rough road.

Another suggestion is violent vomiting attacks. Müller experimenting with an artificial uterus and prepared fetuses produced twists by sudden violent shaking movements, but slight movements such as would occur in the living subject during pregnancy did not produce twisting or knotting.

#### PROGNOSIS

As indicated before, there is little or no risk to the mother in this condition. Although it might be expected, collision of twins during delivery did not occur. Eclampsia was mentioned four times and one mother died of central placenta previa. Neither of these complications could be ascribed to the fact that the twin pregnancy was mono-amniotic.

For the fetuses, however, monoamniotic twinning is of serious import. Of the 109 authentic instances here reviewed, both twins survived in only 17 cases, a 15½ per cent chance. Both twins died in 41 cases and one died in 20 pregnancies, there were 8 monsters to be added to the mortality column, in 23 cases the mortality was not stated, however, 8 of this number resulted in abortions, leaving 94 cases from which to estimate the mortality. Ninety-four twin pregnancies mean 188 babies, 126 did not survive, leaving a death rate of 68 per cent.

#### TREATMENT

Intelligent management presupposes a correct diagnosis. This is rarely made sufficiently early to be of value. If diagnosed after the birth of the first twin by the absence of a second rupture of the membranes, the second twin should be delivered immediately to prevent cord accidents, the usual cause of death.

#### SUMMARY

1. Monoamniotic twin pregnancy is of rare occurrence; only 109 authentic cases were found by me.
2. The prognosis for the fetuses is unfavorable as shown by a 68 per cent mortality.
3. The bad prognosis is due almost entirely to knotting and twisting of the umbilical cords.

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26 SOUTH GOODMAN STREET

## THE "COLD TEST" IN PREGNANCY\*

### A PRELIMINARY REPORT OF ITS USE IN PRENATAL CARE

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WAGENER has shown that changes in the retinal arterioles usually keep pace with increase in hypertension in cases of toxemia of the latter months of pregnancy. The first change is narrowing of the lumens of the arterioles, resulting from spasm or spastic constriction. As the toxemia and blood pressure increase, this constriction may become fixed, and in the retina occur other changes which are recognized as characteristics of the retinitis of the toxemia of pregnancy. The initial retinal changes suggest that the normal balance of the autonomic nervous system has been disturbed, and that vasomotor imbalance of the entire arteriolar bed has occurred.

Evidence indicates that an incipient rise in blood pressure is the earliest sign of beginning preeclamptic toxemia, and the severity of the toxemia is usually considered to be in direct relation to the degree of hypertension. Exceptions occur, however. It would be advantageous, if by some test it might be possible to determine the presence of vasomotor imbalance before onset of the usual symptoms of toxemia of pregnancy or at least to determine with what frequency this vasomotor imbalance occurs during pregnancy.

Hines and Brown, in studying the subject of hypertension from the standpoint of the internist, devised a type of standard stimulus whereby the pattern of reaction of the vasomotor system could be determined. This is known as the "cold test," and the technic of it is as

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follows: The subject remains recumbent for fifteen minutes, or until the blood pressure has attained or approximated the basal level. In cases of hypertension as long as forty-five minutes may be required. With the cuff of the sphygmomanometer placed on one arm, the hand on the opposite side is placed in water that is at a temperature of  $4^{\circ}$  to  $5^{\circ}$  C.; the blood pressure is taken at the end of thirty seconds and again at the end of sixty seconds. The hand is removed from the water and readings are taken every two minutes until the blood pressure has returned to its previous basal level. The highest reading obtained is recorded as the measure of the response.

The originators of the test reported that there is a response of both systolic and diastolic pressure, but that the response of the latter is somewhat less than that of the former, and is more variable. They considered that the response to cold has a purely reflex basis, because

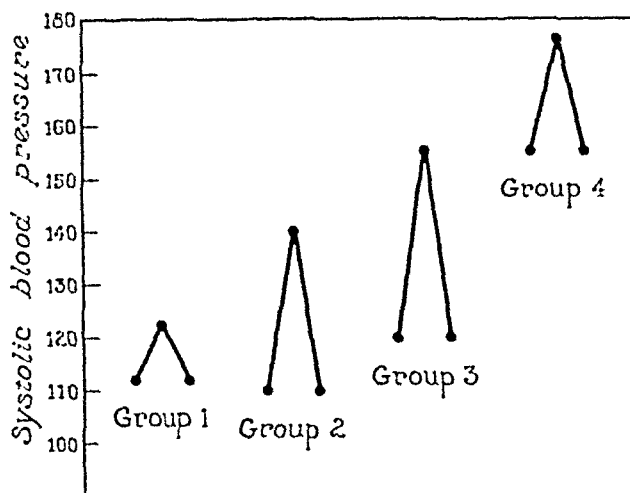


Fig. 1.—Response to cold test. The groups are described in the text, and are designated briefly in Table I.

the reaction is so rapid that any known hormonal or chemical factor could not be concerned. A tourniquet, producing stasis of the flow of blood in the arm that is immersed, fails to inhibit the reaction.

Hines and Brown did not apply their test to pregnant women, but we thought that it should be applied, in the prenatal period, to a sufficient number of patients to prove or disprove its value in forecasting preeclamptic toxemia.

#### MATERIAL AND RESULTS

Reactions to the cold test, numbering 130, were determined on 104 pregnant women who were divided into five groups. Results in four of the groups are given in Table I and Fig. 1. Composition of the groups was as follows:

*Group 1.*—Among the sixty-five women in this group, no evidence of toxemia of pregnancy had appeared by the time of performance of the tests represented in

Line 1 of Table I, nor had such signs appeared at the time of writing of this paper. These women gave normal responses to the tests.

Hines and Brown found a mean rise of systolic pressure of 8.62 mm. of mercury and a mean rise of diastolic pressure of 8.14 mm. of mercury in studies of the normal male and of the normal, nonpregnant female. They considered 15 mm. of mercury as the maximal rise for normal persons, for the range of their readings in this group was between 5 and 15 mm. of mercury. The range in our normal group was slightly higher, so that we accepted 20 mm. of mercury as the maximal reaction of the normal female in the prenatal period.

TABLE I. RESPONSE OF PREGNANT WOMEN TO COLD TEST OF HINES AND BROWN

GROUP		PATIENTS	BLOOD PRESSURE, MM. OF MERCURY			
			MEAN RISE		MEAN BASAL	
			SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
1	Normal response to test; no toxemia to time of writing of paper	65	10.3	10.7	112	67
2	Exaggerated response to test; no toxemia to time of writing of paper	14	30.0	22.5	110	65
3	Exaggerated response to test; toxemia between time of performance of test and time of writing of paper*	7	35.2	26.0	120	77
4	Toxemia at time of performance of test*	8	21.0	10.0	155	94

\*Four of the patients included in this group were also included in the other group indicated by an asterisk. Results with fourteen other patients are recorded in the text. Thus the total of patients was 104.

*Group 2.*—None of the fourteen women in this group had given evidence of toxemia of pregnancy by the time of performance of the tests represented in Line 2 of Table I, nor had such signs appeared at the time of writing of this paper, even though one of the patients had been confined. The patients, however, did give exaggerated responses to the tests.

*Group 3.*—Among the seven women of this group, no evidence of toxemia of pregnancy had appeared by the time of performance of the tests represented in Line 3 of Table I, but all of the seven women had given signs of toxemia before the time of writing of this paper. These patients also gave exaggerated responses to the tests. Of three of these seven patients, reactions when first determined, were within normal limits, but they became exaggerated later in pregnancy, before onset of the signs of toxemia.

*Group 4.*—The eight women in this group had given signs of toxemia of pregnancy before the time of performance of the tests represented in Line 4 of Table I.

We are not prepared at present to try to evaluate the reaction to the cold test of patients, such as these in this group, who have toxemia of pregnancy at the time the test is performed.

*Group 5.*—A group of fourteen patients who gave no symptoms of toxemia, reacted in a manner which does not correspond to any of the reactions obtained by Hines and Brown. This reaction consisted in a persistent fall from the basal levels, of both systolic and diastolic pressures, during the period of immersion of the hand in cold water. In some of these cases, the fall persisted after removal of the hand, and in others the pressures rose to approximate the basal levels within two minutes. In two cases in which fall of the blood pressure was persistent, there was an asso-

ciated sense of faintness, which disappeared as the blood pressure rose. This represents essentially an inverted reaction for which we have no explanation at present. Swelling of the immersed hand, or other symptoms which might be associated with cold allergy, did not appear. The symptoms related may be as significant of vasomotor imbalance as is the exaggerated reaction of blood pressure but so far none of this group of fourteen patients has shown any signs of toxemia of the latter months of pregnancy. The basal blood pressures were 117 mm. of mercury systolic, and 75 mm. diastolic. The mean fall in systolic pressure was 11.2 mm. of mercury and that of the diastolic pressure was 6 mm.

#### COMMENT

In attempting to apply this standard test of measuring the variability of blood pressure in the prenatal period, the only values we have for comparison deal with the general problem of hypertension. Although the exact cause of elevation of the blood pressure is not yet determined, it is felt that the hypertension associated with toxemia of the latter months of pregnancy is related to a toxin which affects the whole maternal organism. We have evidence that preclampsitic toxemia is associated with spastic constriction or with contraction of the arteriolar system, through observations made on the arterioles of the retinas of patients suffering from this condition. This constriction or contraction may be related to a particularly reactive vasomotor system. It is possible that a pregnant woman who manifests an exaggeratedly reactive vasomotor system in response to the cold test is more likely to suffer from toxemia of the latter months of pregnancy. It is significant that in no case in which the response to the cold test has been persistently normal, has toxemia developed, and that in all cases in which toxemia has developed a hypertensive reaction has been demonstrated.

Of the patients who have manifested a definitely exaggerated reaction (Groups 2 and 3, Table I), 33 per cent have presented the usual signs of toxemia in the latter months of pregnancy.

This paper is presented as a preliminary report. More studies are to be made on the patients already under observation and the number of patients is to be enlarged.

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*Estes, Jr., and Heitmeyer*: *Pregnancy Following Ovarian Implantation*, *Am. J. Surg.* 24: 563, 1934.

After bilateral salpingectomy an ovarian implantation had been done in which the cut surface of the ovary, still attached to its pedicle, was implanted upon the cut surface of the uterine horn. Of 50 patients operated upon in this manner, whose records are complete, four (8 per cent) became pregnant, two had abortions at about the third month and two had full-term pregnancies.

J. THORNWELL WITHERSPOON.

## THE USE OF PARALDEHYDE IN OBTAINING OBSTETRIC ANALGESIA AND AMNESIA\*

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EACH of the existing methods of obtaining analgesia and amnesia during labor has some objectionable features. Ether mixtures tend to cause asphyxia of the baby. Barbiturates usually produce amnesia only; the fact that there is little or no actual pain relief is shown by the marked restlessness which attends each uterine contraction. Scopolamine is a drug of high toxicity, is not analgetic, and only in combination with other drugs is it sufficiently powerful to produce amnesia.

Drugs administered hypodermically are beyond control once they are given. Oral medication is frequently impossible because of the tendency of patients to vomit during labor. Many solutions designed for rectal instillation are not well retained as they cause irritation of the mucosa.

The procedures which will be described in this paper are the results of repeated pharmacologic experiments and clinical tests performed in an attempt to secure relief and forgetfulness of pain by the use of drugs of the lowest toxicity, drugs which cause the least excitability and are the least likely to cause harm to mother or child.

The flexibility and wide safety range of paraldehyde suggested its employment as the basic factor around which the technic might be developed. Rectal administration was chosen, as the solution may thus be given to an unconscious patient. In order to facilitate retention of the paraldehyde, the rectal mucosa is anesthetized by the addition of benzyl alcohol. As benzyl preparations have the power to relax unstriated muscle, it was believed that it would allow more rapid dilatation of the cervix. Laboratory and clinical observations have seemed to prove that this is true.

Paraldehyde is not a complete analgesic as pain impulses evidently reach the brain even though the patient be unconscious. In our early cases we attempted to block pain conduction by giving amidopyrine intramuscularly, but the results did not warrant its continuation. An occasional dose of morphine will augment the action of paraldehyde

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when proper analgesia is not being obtained. Opium derivatives are said to be particularly dangerous to the fetus through depression of the respiratory centers. Personal experience with morphine, however, has convinced us that the incidence of asphyxia caused by this drug is grossly exaggerated.

Resenstein and Davidoff, Bartholomew and others have found paraldehyde to be of value in relieving the pain of labor, but they have used it in connection with various barbiturates, a group of drugs which we have avoided because of our belief that they are dangerous in the dosage required.

In addition to the clinical observations to be reported in this paper, experiments upon the uteri and cervixes, extirpated and in situ, of several species of laboratory animals have been made. A detailed account of this work, from a pharmacologic viewpoint, will be published in a future communication, but at this time only the clinical results will be presented.

Disregarding the first twenty or thirty cases in which we were endeavoring to learn the optimum dosage and technic, we offer our observations in a series of 175 cases of labor in which the method has been employed.

#### TECHNIC OF ADMINISTRATION

At the beginning of labor, the rectum is emptied by a soapsuds enema, followed by tap-water irrigation until the return is clear. This is a particularly important step in the technic. In five cases excitement was present to the point of requiring restraint. In each case it was found that the rectum contained a large amount of fecal matter which undoubtedly interfered with the absorption of the solution.

As soon as the patient says that the contractions are painful, regardless of the state of the cervix or the interval between pains, the treatment is started.

The most satisfactory dose of paraldehyde has been found to be 1 c.c. to each  $8\frac{1}{2}$  pounds of the patient's weight. For practical purposes it is sufficiently accurate to give 1 c.c. to each 10 pounds and add 2 or 3 c.c. To the paraldehyde is added 1.5 c.c. of benzyl alcohol. This mixture is instilled into the rectum by gravity through a large catheter and is followed by one ounce of salt solution to wash it out of the tube. If the patient is not asleep in thirty minutes,  $\frac{1}{4}$  gr. of morphine is given hypodermically. Should the patient be awake one hour after the morphine injection, the original dose of paraldehyde and benzyl alcohol is repeated. Usually, however, the rectal medication need not be repeated for several hours. The patient sleeps soundly, perhaps stirring with each pain. In many cases the only evidence of uterine activity is the seeing or feeling of the contractions by the observer. As the effect of the drugs begins to wear off, the patient becomes slightly restless and may complain of discomfort but falls asleep immediately after each pain. At this time the rectal injection is repeated. The effect of each dose lasts from two to five or six hours, three hours being the average duration. Occasionally, when the repeated dose does not give prompt results,  $\frac{1}{4}$  gr. of morphine is given fifteen to thirty minutes later. When the presenting part reaches the perineum, delivery is accomplished by outlet forceps under ethylene anesthesia.

The objects sought for in the use of these procedures are analgesia and amnesia without endangering mother or child, adding to the length of labor or causing undue excitation of the patient.

Evaluation of results shows that the degree of success varies with the length of labor. In the case of a multipara in labor only for one or two hours, this method of treatment is practically useless; to the primipara with a slowly progressing posterior position it is a very great relief.

In estimating the length of labor, it has been necessary to disregard the usual division into first and second stages. In most instances one stage merges imperceptibly into the other, and frequently the bulging perineum has been the first indication of full dilatation of the cervix. Observation of these cases has strengthened our belief that the voluntary contractions of the abdominal muscles are of no great importance in the second stage of labor. We have practically abandoned the practice of having the patient "bear down" and pull on straps. For the perineal stage, anesthesia is necessary. In this series, ethylene has been used in the majority of cases. When it has been impossible to secure the services of an experienced anesthetist, ether has been given.

As it is our custom to deliver by outlet forceps practically all heads that reach the perineum, to rotate and deliver all posterior occiputs if progress ceases for one hour and to extract all breeches when the cervix is dilated, our operative incidence has not been increased. As the patient is unconscious and therefore cannot cooperate, instrumental aid at the perineal stage is practically always necessary.

The patients usually sleep soundly for six or eight hours after delivery. No ill effects on the mother have been noted. The pulse rate, blood pressure, and respirations remain unchanged. Urinalysis has shown no kidney damage. While no case of serious cardiac disease has been found in this series, several patients with symptomless murmurs have been carried through labor with complete success. Toxemia, nephritic or hepatic, seems to be no contraindication to the use of this method, as several cases of this type showed no ill-effects. Postpartum bleeding has not been increased. Records of animal experiments in the laboratory have confirmed these clinical observations.

When ethylene has been used during delivery, the babies have breathed and cried as promptly as in cases where no analgesic agent had been employed. Several cases of delayed breathing but not dangerous asphyxia have occurred when it had been necessary to use ether for delivery.

In the laboratory it was learned that paraldehyde slightly decreased the force of uterine contractions and that benzyl alcohol seems to relax the cervix. As the average labor in this series was much shorter than the accepted normal figures, it would seem that the softening of the cervix more than offsets the diminution in power of the contractions.

The results in regard to analgesia and amnesia separate the cases into four groups. Group A consists of cases in which analgesia is considered to have been adequate and amnesia complete. The patients in Group B are those who move about and complain of pain. Many of these patients seem to be entirely rational, at times. Amnesia, however, in this group is complete. Patients who remember having had pain, but who have undoubtedly been markedly relieved, constitute Group C. In Group D are those who received no benefit whatever.

Of 94 primiparas, 59 are in Group A, 29 in Group B, 3 in Group C, and 3 in Group D. Of 81 multiparas 32 are in Group A, 29 in Group B, 11 in Group C, and 9 in Group D. All of the patients in Group C were in labor less than four hours and those in Group D less than two hours. The duration of labor as estimated from the time of the first dose of the rectal solution until delivery was started varied, in primiparas, from one to thirty-eight hours. Labor in multiparas lasted from one-half to fourteen hours. Sixty-seven, or 71 per cent, of the primiparas and 68, or 34 per cent, of the multiparas were in labor less than ten hours. From one to six rectal injections were given, the average number being two in primiparas and one in multiparas. Morphine was used at the beginning of labor in 122 cases and was repeated in 48.

TABLE I

	GROUP A AMNESIA AND ANALGESIA	GROUP B AMNESIA AND PARTIAL ANALGESIA	GROUP C PARTIAL AMNESIA AND ANALGESIA	GROUP D LITTLE OR NO RELIEF
Primiparas	59	29	3	3
Multiparas	32	29	11	9
Total	91	58	14	12

## CONCLUSIONS

1. The combination of paraldehyde and benzyl alcohol produces satisfactory analgesia and complete amnesia in practically all cases in which labor is of more than four hours' duration.

2. This solution is retained, having been expelled only in cases in which the presenting part was pressing on the rectum. It does not cause vomiting.

3. No ill-effects have been noted in either mother or child.

4. Having been spared the psychic shock of pain, the memory of suffering and fatigue from bearing down and straining during the second stage, the patient awakens from her long postpartum sleep actually refreshed.

5. The method here described is not perfect, but it seems to accomplish more with fewer disadvantages, than any other of the existing methods of relieving the pains of labor.



## A STUDY OF CARCINOMA OF THE CERVICAL STUMP DEVELOPING AFTER SUBTOTAL HYSTERECTOMY\*

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THE occurrence of carcinoma as a primary lesion in the cervical stump after subtotal hysterectomy was first mentioned by Chrobak<sup>1</sup> in 1896. The earliest attempt toward a more comprehensive study upon this subject was the work of Condamin,<sup>2</sup> whose publication appeared in 1902.

Gilbert,<sup>3</sup> Hochman,<sup>4</sup> and others have reported that carcinoma develops in the cervical stump of 0.3 per cent to 2 per cent of the patients subjected to supra-cervical hysterectomy. The low incidence would not justify the greater mortality rate of total hysterectomy as a generally accepted routine. However, complete removal may be indicated in patients presenting badly lacerated or inflamed cervixes with some other lesion of the corpus. The importance of careful diagnosis before operation is illustrated by the combined statistics of Schottlander, Spencer, and Noble, reported by Polak.<sup>5</sup>

The difficulties encountered in the treatment of patients with carcinoma of the cervical stump and the poor results invariably reported by all authors, have also been responsible for the active interest displayed in this problem. The anatomical distortion due to the previous laparotomy has rendered adequate surgical removal extremely hazardous. This has in general relegated the treatment of these patients to radiation. The poor results obtained from radiation have been attributed to the absence of the uterine corpus, which may prevent a correct application of radium for a sufficient dose. It has been intimated that as a result of faulty applications normal tissues are frequently overirradiated, and that peritoneal accidents are apt to occur. The absence of the uterine corpus would not seem to increase materially the complications from external irradiation. Healy<sup>6</sup> has repeatedly emphasized the importance of roentgen irradiation for the treatment of parametrial disease, and he has pointed out that an adequate dose of radium applied to the cervix is capable of controlling the disease only in and directly adjacent to the cervix. In the statistical reports that have been published upon the treatment of carcinoma of the cervical stump, sufficient external irradiation has seldom been employed.

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To classify any patient as one in whom carcinoma developed in the cervix after the uterine corpus had been removed, one must ascertain whether or not disease was present at the time supracervical hysterectomy was performed. It is impossible to be completely informed as to the clinical and histologic appearance of the cervix at the time of previous operation in each suspected instance. The time factor, therefore, must serve as the criterion of selection. That is, the interval elapsing between the removal of the uterine corpus and the development of carcinoma must be sufficient to remove all reasonable doubt that a malignant tumor was not present at the time of operation. Upon this basis the cases selected for this series were those in which at least one year elapsed following operation before symptoms of cervical carcinoma appeared, or in which at least three years elapsed before the diagnosis of carcinoma was made.

Zampa<sup>7</sup> states that the incidence of stump carcinoma among all patients with malignant disease of the cervix has been variably reported from 0.2 per cent to 4 per cent.\* Among the 2,600 patients admitted to the Gynecological Clinic of Memorial Hospital from January, 1920, to July, 1933, with the diagnosis of carcinoma of the cervix, 67 pa-

\*Since the presentation of this paper, von Graff (AM. J. OBST. & GYNEC. 28: 18, 1934) has published a comprehensive report upon carcinoma of the cervical stump. In a collected series of 4,269 patients with cervix cancer he found the average incidence of stump cancer to be 4.1 per cent. However, in some of the individual clinics that were quoted, the incidence was much greater, and von Graff believes that carcinoma of the cervical stump may occur more frequently than is commonly recognized. The material he reported included patients in whom carcinoma was present at the time of subtotal hysterectomy, as well as those in whom carcinoma developed as a primary lesion in the cervical stump after removal of the uterine corpus. Of 551 patients upon whom there was sufficient data, 23.5 per cent had carcinoma of the cervix at the time of operation. He presents a plea for total hysterectomy as a prophylactic measure, because most stump cancers are epidermoid in character, and destruction or removal of the cervical mucosa by coning out, etc., has failed to prevent its occurrence. He also states, that "properly performed, both in the literature and my own experience testify that the operative mortality is not considerably higher."

Pearse (Surg. Gynec. Obst. 58: 845, 1934) contends that the possibility of carcinoma developing in the cervical stump should not be considered as an indication for total removal of the uterus, unless the mortality for this operation can be shown to be the same or less than for supravaginal hysterectomy. He reported an operative mortality of 1.7 per cent among 1,900 patients upon whom subtotal hysterectomy had been performed. Pearse also published statistics that have been quoted by von Graff, as well as those from other clinics, as follows:

	PERCENTAGE OPERATIVE MORTALITY	
	TOTAL HYSTEREC- TOMY	SUBTOTAL HYSTEREC- TOMY
Welbel	3.55	4.25
Amreich	3.8	1.7
Shaw	5.9	3.05
Fullerton and Faulkner	4.1	4.4
Masson	1.3	1.8
Mayo	1.8	1.2
Burch and Burch	3.1	4.2
Bartlett and Simmons	5.1	

Of the 1,900 patients from whom the uterine corpus had been removed, Pearse was able to trace 810 for a period of five or more years. The incidence of stump carcinoma among the patients who were followed was 1 per cent.

The average of the collected statistics quoted by von Graff revealed that 0.62 per cent of patients treated by subtotal hysterectomy developed carcinoma in the cervical stump at some later date. The greater incidence of stump carcinoma among all cases of cervix cancer is undoubtedly due to the failure of recognizing the presence of the disease at the time of operation. Von Graff has stated, that among the patients upon whom he had sufficient data, 23.5 per cent had carcinoma of the cervix at the time subtotal hysterectomy was performed.

tients, or 2.6 per cent of the entire number, were found who had developed malignant disease in the cervical stump. From three to ten years intervened between subtotal hysterectomy and the diagnosis of carcinoma in 48 per cent of the cases, and from ten to twenty years in 37 per cent. In 15 per cent the disease was not recognized until twenty to thirty-seven years after laparotomy.

TABLE I. NUMBER OF YEARS INTERVENING BETWEEN SUBTOTAL HYSTERECTOMY AND THE DIAGNOSIS OF CARCINOMA IN THE CERVICAL STUMP

	YEARS AFTER SUBTOTAL HYSTERECTOMY			
	3 TO 10	10 TO 20	20 TO 30	30 TO 37
Number of patients	32	25	7	3
Percentage	48	37	10.5	4.5

A survey of this group of 67 patients shows them comparable in age, clinical extent of disease, histologic grouping, and symptomatology with the other cases of cervical carcinoma reported by Healy.

The extreme age limits were twenty-three and sixty-seven years. Thirty-six per cent of the patients were between forty and fifty years of age, and 42 per cent were found to be from fifty to sixty years old.

There were 18 patients, or 27 per cent of the series, who were classified as having early or borderline disease, forming a group with a favorable prognosis. Forty-nine patients, or 73 per cent, had advanced lesions, and presented an unfavorable prognosis.

Histologic diagnosis had been made in all of the 67 patients except two. One of these applied to the clinic in a condition too far advanced for treatment, having already developed a vesicovaginal fistula. The other patient survived three years after treatment and died of carcinoma metastases and pelvic peritonitis. Among the 65 patients with histologic data 61, or 94 per cent, were epidermoid in type. Four patients, or 6 per cent, were found to have glandular carcinoma. Of the epidermoid lesions 18 per cent were classified as Group I, 72 per cent as Group II, and 10 per cent as Group III.

Monod<sup>s</sup> reports a preponderance of the glandular variety of carcinoma among those patients developing carcinoma in the cervical stump within a short time after removal of the corpus uteri. This would seem to indicate that malignant disease had been present at the time of operation, and was probably located in the endometrium. The four cases of adenocarcinoma included in the series reported here were diagnosed six, sixteen, nineteen, and thirty years after hysterectomy. This long interval between operation and the recognition of adenocarcinoma in the cervical stump indicates that the disease had developed in the cervical glands, or remaining lower uterine segment after removal of the corpus. This further substantiates the contention that as far as can be determined, the patients included in this series

represent cases in whom primary carcinoma developed in the cervical stump after subtotal hysterectomy.

The clinical symptoms for which the patients presented themselves were identical to those usually noted in carcinoma of the cervix. Bleeding and actual hemorrhage were present in 74 per cent. Bloody discharge was noted in 24 per cent, and leucorrhea alone occurred in 2 per cent. Pain was a rather conspicuous feature among the patients with an unfavorable prognosis. It was usually located in the lower back over the sacrum, and radiated into the hips.

It might be supposed that patients who had already undergone surgical treatment for a major pelvic disorder would report for medical attention promptly after the occurrence of gynecologic symptoms. This was not found to be true in this series however, since the patients did not present themselves for treatment any earlier than other cases of cervix carcinoma. In a review of 100 patients with cervix cancer, 65 per cent received treatment within a year after they first observed symptoms of an intravaginal disturbance. Sixty per cent of the stump cases were seen within a year after the onset of symptoms. The importance of educating the public to seek medical advice upon the appearance of unusual signs or symptoms cannot be overestimated in the attempt to control cancer.

Pinsan<sup>9</sup> states that in most cases of carcinoma of the cervical stump, subtotal hysterectomy has been performed for fibromyomas. This is to be expected since a large percentage of corpus amputations are done for the removal of myomatous uteri. In our series 58 per cent of the patients had been operated upon for this condition. Other indications for previous surgery were, bleeding uteri, pelvic inflammatory disease, benign ovarian disorders, and prolapse of the uterus. These data afford no additional information concerning the etiology of carcinoma developing in the cervical stump.

Polosson<sup>10</sup> and Monod<sup>8</sup> have suggested the possibility that resulting alteration in the physiologic and anatomical conditions caused by operative interference may predispose tissues of the cervical stump to the development of carcinoma. An isolated cervix is often seen to undergo regression in size and to assume senile characteristics. However, it is impossible to state whether or not this has any influence upon the development of malignant tumors. It has been generally agreed that carcinoma of the cervix is associated with multiparity. The high incidence of fibromyomas and the history of other pelvic disorders in all of the patients in this series, suggest that sterility may have existed in some of the patients. All of the patients were married, but 9 per cent had never been pregnant. As nearly as could be determined from the available data, about 85 per cent had been delivered between midterm and term. In a similar study of 46 patients Branscomb<sup>11</sup> found that only 80 per cent had borne

children. In all cervix cases from 90 to 94 per cent of the patients have a history of preceding childbirth.

Monod<sup>8</sup> states that less than 15 per cent of all patients with carcinoma of the cervical stump are cured. He believes that the best statistics so far published have come from the Institut du Radium in Paris. Among the 27 patients observed at that institution, 10 were reported living for two to ten years after treatment.

At the Memorial Hospital all of the patients have been treated by radiation except three, who received no treatment because of their hopeless prognosis. Examination of the yearly survival in the 64 treated patients shows that the best results have been obtained over the past seven or eight years. This may be due to the fact that high voltage roentgen ray was used in addition to radium in most instances.

From 1929 to the present time 28 patients have been treated. The yearly survival among these patients has been sufficiently improved to indicate that a greater total salvage may be obtained. The prospects of better results in this group may be attributed to the greater amount of external irradiation which the patients have received. The roentgen ray cycle administered before the radium treatment was given has been particularly important. By this means the cervix has been better prepared for the application of radium, because the infection is diminished, and regression of the lesion lessens the trauma of placing radium within the canal.

The five-year salvage of the 36 patients who were treated five or more years ago is 14 per cent. This result compares favorably with the statistics reported from other clinics. However, the percentage survival among patients with cancer of the stump is lower than it is in all patients with cervix cancer treated at Memorial Hospital. Comparison of the five-year results obtained in the treated patients of the two groups illustrates the difference. Among the patients with early disease 43 per cent of those with stump cancer survived, while 50 to 60 per cent of all patients with the same degree of disease involvement have survived for this period of time. In those with advanced disease 7 per cent of the patients with cancer of the stump lived for five years, as opposed to from 10 per cent to 15 per cent of all cervix cases. The total five-year salvage shows the same discrepancy. Only 14 per cent of the 36 patients with stump cancer treated before 1929 lived for five years, as compared with 20 to 24 per cent of all cervix cases.

The poor results obtained in patients with carcinoma of the cervical stump may be partially explained by the anatomical difficulties encountered in making a correct application of radium. The usual tandem employed in the treatment of cervix cancer cannot be used because of the absence of the uterine corpus. In most patients with stump cancer a single capsule can be placed in the canal of the remaining vaginal

portion of the cervix. However, in many patients the cervix has been partially destroyed by the disease, and the radium can only be packed into an ulcerated crater. In the latter instance the radium is frequently left in place for a lesser dose than would ordinarily be used, in order to protect the bladder and rectum from an excessive amount of radiation. Also, a lesser tissue dose is obtained because of the poorer distribution of radiation from such a faulty application. This of course results in inadequate treatment for these patients. It should again be mentioned that radium applied to the cervix is capable of controlling the disease only in and directly adjacent to the cervix. External irradiation must be relied upon for adequate treatment of malignant disease beyond this region. The absence of the uterine corpus should not interfere with the use of roentgen radiation, which may also be used to supplement the treatment of the primary lesion.

Another possible explanation of the poor results obtained in patients with stump cancer is the fact that the carcinoma is located in scar tissue resulting from the previous hysterectomy. The tumor may be accustomed to a poor blood supply before treatment is begun. In such a condition the radiosensitivity of the lesion would be affected, because the sclerosis of blood vessels is an important factor in the causation of tumor regression by radiation.

Whether the presence or absence of ovaries influences the response of the tumor to radiation is unknown. There were 16 patients in the series who were known to have had both ovaries removed. These patients were distributed throughout all the age groups. Seven were classified as having a favorable prognosis and 9 had advanced disease. The yearly survival of these patients was not found to be different from their respective groups, nor was the combined salvage rate different from that of all stump cases.

In an analysis of the treatment given to patients with carcinoma of the cervical stump, it is necessary to consider the dose delivered to each individual.\* For a comparison some unit representing an amount of radiation must be employed. The so-called "threshold erythema" serves very well for this purpose. This has been defined by Quimby<sup>12</sup> as representing an amount of radiation which will produce a visible reddening of the skin in 80 per cent of the individuals receiving the exposure, and no visible reaction in the remaining 20 per cent. While the definition originally related to external irradiation by x-rays or radium, it has been extended by Quimby and Martin<sup>13</sup> to interpret dosages from interstitial sources of radium, such as seeds, needles, tandems, etc.

The dose obtained in the cervix has been chosen for the comparison of the treatment given to the different patients, because it represents

\*Tissue doses have been calculated by Mrs. Edith H. Quimby of the Department of Biophysics, of Memorial Hospital.

the primary lesion. Also, it is in the cervix that the results of irradiation can be visually appreciated. The changes in the primary lesion are important for estimating the clinical result, especially as regards the healing of the cervix, or so-called "primary cure." In calculating the dose each patient received, the amount of radiation delivered to the primary lesion by the use of radium locally and by external irradiation has been considered.

In most patients the bulk of the cervix can be included in a sphere 3 cm. in diameter. This volume would also approximate the average size of the primary lesion among those patients in whom the portio vaginalis had not been destroyed by the tumor process. For each patient, the tissue dose was calculated in terms of threshold erythemas for a point on the periphery of the sphere. This point was 1.5 cm. lateral to the canal at a depth of 1.5 cm. in the cervix. The deter-

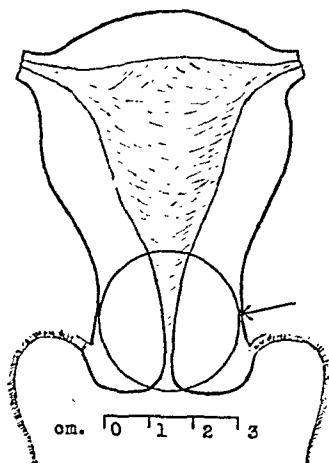


Fig. 1.—Diagrammatic illustration of the point chosen for the calculation of the minimum tissue dose delivered to the primary lesion.

mined dose then represented the minimum quantity of radiation delivered to any point within this volume. In other words, this would be an approximate value of the minimum tissue dose delivered within the primary lesion.

For individuals in whom the malignant disease had eroded a crater, or destroyed the cervix, the procedure was not so simple. In calculating the dose these patients received, a sphere 3 cm. in diameter could not be considered as representing the size of the primary lesion. It was necessary, therefore, to determine its size and the volume throughout which the radium was distributed, as accurately as possible from the description contained in the patient's clinical record. The dose delivered to the primary lesion could then be calculated on a comparable basis with the other patients. The estimation of tissue doses under any circumstance is only approximate, but such a procedure does offer an excellent measure for the comparison of treatment in different individuals.

In both the favorable and unfavorable groups the patients were divided into subgroups according to the tissue dose that had been delivered to the primary lesion. The yearly survival for each subdivision was then determined, depending upon the percentage of living patients among those who had come under observation for the specified number of years. For instance, a patient first observed in 1930, or three years ago, would appear under the first, second, and third years, but not under the fourth. Because of the small number of patients in each subgroup the percentage survival has been converted into the nearest number divisible by five.

In the patients with a favorable prognosis the malignant disease was largely confined to the cervical region, as far as could be determined from clinical examination. A good result could, therefore, be expected in most cases from the application of radium to the cervix alone, provided a lethal tumor dose was delivered. The minimum dose any of these patients received in the primary lesion was from 4 to 6 threshold erythemas. The small number of patients in each of the subgroups representing various doses of radiation does not justify any definite conclusion upon the effect of different amounts of treatment. However, the fact that a primary cure was obtained in every patient except one in the group that received a minimum dose of 6 to 8 threshold erythemas, and the fact that in no case did disease reappear in the cervix after a primary cure had been obtained, indicates that adequate treatment was given to the cervical region in most instances in this group.

All of these patients lived for at least two years after treatment. This excellent result may be attributed to the early stage of the disease, and the relatively high minimum dose delivered to the primary lesion. It seems logical to assume that the loss of patients after the second and third years following treatment may be attributed to uncontrolled disease located at a distance beyond the range of radium applied to the local lesion. There were only 3 patients who received as much as 2 threshold erythema doses in the parametrial regions. This dose was obtained by roentgen irradiation, and has no relation to the tissue dose discussed for the primary lesions. Two of these patients were treated only a year ago, but the third is living and free of disease four years after treatment. This isolated patient tends to illustrate that a better salvage might be expected if this method of treatment were employed more vigorously.

In the analysis of the advanced cases 6 patients have not been included. Three of these received no treatment because of their hopeless prognosis, as has been stated before. Two were not included because they failed to return for the completion of their treatment. One patient has been treated too recently to warrant any comment upon the result obtained. However, analysis of the remaining 43



TABLE II. CLASSIFICATION OF THE 18 FAVORABLE CASES ACCORDING TO THE AMOUNT OF RADIATION DELIVERED TO THE PRIMARY LESION

THRESH- OLD ERYTH- EMA DOSES		YEARS SINCE TREATMENT										PRI- MARY CURE	RE- NEWED ACTIVITY IN CERVIX
		1	2	3	4	5	6	7	8	9	10		
4 to 6	Number of patients	5*	3	2								(5)	(0)
	Per cent survival	100	100	50								100%	
6 to 8	Number of patients	4*	3	3	2	2	2	2	2			(3)	(0)
	Per cent survival	100	100	100	50	50	50	50	50			75%	
8 to 12	Number of patients	9	9	8	7*	5	4	2	2	2	1	(9)	(0)
	Per cent survival	100	100	85	55	40	25	-	-	-	-	100%	

\*Indicates a patient who received as much as 2 threshold erythema doses in the parametrial regions from external irradiation.

patients with advanced disease has proved more instructive than the study of the favorable cases, because of the wider variation in the amount of radiation they received, and the larger number of patients in each treatment group.

The yearly survival rate increased with the amount of treatment delivered to the primary lesion. Among the patients who received a minimum dose of 1 to 4 threshold erythemas, only 75 per cent survived the first year. If a minimum tissue dose of 4 to 6 threshold erythemas was delivered to the primary lesion, 85 per cent lived for that time, and with greater amounts of treatment from 90 per cent to 100 per cent survived one year. In the same order the four-year salvage increased from 15 per cent of those who received the smallest amount of radiation four or more years ago, to 30 per cent or 40 per cent if they received a minimum dose of more than 6 threshold erythemas. None of the patients treated five or more years ago who received less than 6 threshold erythema doses in the primary lesion lived longer than four years. However, among those with a tissue dose of 6 to 8 threshold erythemas, one patient lived for five years, and another in the group that received 8 to 12 threshold erythema doses is still living and free of disease for the same period of time. These 2 patients among the 12 who received a minimum tissue dose of 6 threshold erythemas at least five years ago, represent a five-year salvage of 15 per cent. This result is comparable to that obtained in all patients with cervix cancer with advanced disease.

Definitely improved results with heavier treatment can also be illustrated by the number of primary cures that were obtained in the

advanced group. This result occurred in only 35 to 50 per cent of the patients who received less than 6 threshold erythemas as the minimum dose within the primary lesion, but in 75 per cent if more than that amount of radiation was delivered.

The reappearance of malignant disease in the cervix after a primary cure has resulted may be interpreted as evidence that the primary lesion has been insufficiently irradiated. Of the 3 patients who attained a primary cure in the group that received from 1 to 4 threshold erythema doses, there were 2 who developed renewed activity in the cervix. The incidence of such reappearances was reduced to 15 per cent among those who received 4 to 6 threshold erythema doses, and to 10 per cent in those with a tissue dose of 6 to 8 threshold erythemas. None of the patients who received 8 to 12 threshold erythema doses showed activity in the cervix after a primary cure had been obtained.

There were 7 patients among the advanced cases who received 2 threshold erythema doses in the parametrial regions from external irradiation. One of this number was in the group that received a tissue dose of 1 to 4 threshold erythemas in the primary lesion. This patient lived for four years. Two others were among those who received 4 to 6 threshold erythema doses, and survived for two and four years, respectively. There were also 2 in the group that received 6 to 8 threshold erythema doses, both of whom are living for one and

TABLE III. CLASSIFICATION OF 43 ADVANCED CASES ACCORDING TO THE AMOUNT OF RADIATION THEY RECEIVED IN THE PRIMARY LESION

THRESH- OLD ERYTH- EMA DOSES		YEARS SINCE TREATMENT										PRI- MARY CURE	RE- NEWED ACTIVITY IN CERVIX
		1	2	3	4	5	6	7	8	9	10		
1 to 4	Number of patients	9	8	7	7*	7	7	5	5	5	3	(3)	(2)
	Per cent survival	75	50	45	15	-	-	-	-	-	-	35%	65%
4 to 6	Number of patients	12	11*	10	10*	8	8	7	7	5	5	(6)	(1)
	Per cent survival	85	75	30	10	-	-	-	-	-	-	50%	15%
6 to 8	Number of patients	13*	11*	8	7	6	5	5	3	3	2	(10)	(1)
	Per cent survival	100	75	40	30	15	-	-	-	-	-	75%	10%
8 to 12	Number of patients	8	8	8	8	6	4	3	1			(6)	(0)
	Per cent survival	90	75	40	40	15	-	-	-			75%	

\*Indicates a patient who received as much as two threshold erythema doses in the parametrial regions from external irradiation.

two years after treatment. The remaining 2 patients who received this amount of external irradiation were among those with a tissue dose of 8 to 12 threshold erythemas. One of these lived for four years after treatment, and the other is still living and free of disease for the same period of time. It is interesting to note, that 4 of the 7 patients who survived a span of four years after treatment, had received 2 threshold erythema doses in the parametria at about the same time that the radium treatment was given to the primary lesion.

From this study of the yearly salvage in patients with advanced stump carcinoma and of the changes occurring in the primary lesion, such as the percentage of primary cures and the incidence of renewed activity of the disease in the cervix, it is apparent that the best results were obtained in the groups that received the two greater amounts of treatment. The percentage of primary cures among the patients who received a minimum dose of 8 to 12 threshold erythemas was not greater than it was in the group that received 6 to 8 threshold erythema doses. In both of these groups the five-year salvage compared favorably with the results obtained in all patients with advanced carcinoma of the cervix. Therefore, a minimum of 6 to 8 threshold erythema doses delivered throughout the primary lesion probably represents the minimum amount of radiation required for a lethal dose to cervix cancer, when administered at the rate, and by the method used in the treatment of these patients. If the primary lesion requires this dosage, control of parametrial disease no doubt necessitates at least the same amount of radiation. It must be remembered that most of the treatment given to the local lesion in these patients was by radium applied to the cervix. The strength of the radium capsules was sufficiently great to deliver the required dose in about twenty-four hours. Radiation was, therefore, administered at a relatively high intensity. None of the patients received more than 2 threshold erythema doses in the parametrial regions, delivered by two courses of roentgen ray treatment with at least a six-week interval between the two cycles. To deliver 6 to 8 threshold erythema doses to the parametrial disease by external irradiation would necessitate a protracted treatment with multiple small exposures. It is doubtful that 6 to 8 threshold erythema doses delivered at a slow rate of administration would have as marked a biologic effect upon the tumor as the same dose delivered over a short time. Further investigations in the technic and methods of roentgen ray treatment may result in a greater salvage of patients with carcinoma of the cervix, than is attained at the present time.

Complete treatment by the method employed at Memorial Hospital requires about eight weeks. For the past few years the routine treatment for carcinoma of the cervix has consisted of a high voltage pelvic cycle of single exposures delivering 700 roentgens to each of four

pelvic fields. About seven to ten days after the roentgen ray treatment has been completed, a vaginal applicator containing radon is placed against the primary lesion for a dose of 1,500 mc. hours, and an intracervical tandem for 3,000 mc. hours. Six weeks after the radium treatment the roentgen ray cycle has been repeated. By this method the average patient receives a minimum dose of about 7 to 8 threshold erythemas in the primary lesion, and about 2 threshold erythema doses in the parametrial regions. The wide variation in the tissue doses recorded for the primary lesion in the different patients of this series has been due to the difficulties of making a correct application of radium within the cervical canal of some patients.

In order to increase the parametrial dose we have begun a plan of multiple exposures to each of the pelvic fields for a protracted roentgen ray treatment at a different rate of administration.<sup>14</sup> By this means from 4 to 5 threshold erythema doses may be delivered to the bulk of the parametrial regions within a period of three or four weeks. The primary lesion receives about 5 threshold erythema doses from the external irradiation alone. This treatment has been followed by the usual radium applications with encouraging results. By carefully planning the treatment of patients with stump cancer a tissue dose may be obtained that is comparable to the amount of radiation which has been delivered to all other patients with cervix cancers. If adequate treatment is given the total salvage of patients with stump cancer should be raised to equal that of all patients with carcinoma of the cervix.

The constitutional effect upon the patient is important in the consideration of different amounts of treatment. Among the advanced cases in which treatment was completed there were 4 patients who developed fistulas. Three of these were of the vesicovaginal type, and occurred in patients who had received a minimum dose of less than 6 threshold erythemas in the primary lesion. Careful examination of the clinical records of these three patients indicated that the fistulas had resulted from extension of uncontrolled disease. The fourth patient was in the group that received 8 to 12 threshold erythema doses. When the treatment was given, disease was present in the rectovaginal septum where the fistulous tract later developed. The heavy irradiation possibly precipitated the development of the fistula, but disease was so advanced that the patient did not survive the first year. The occurrence of vesicovaginal or rectovaginal fistulas does not seem to be related to overirradiation, as much as it does to the presence or extension of uncontrolled disease.

Dean<sup>15</sup> states that bladder injuries following irradiation for uterine disease usually appear several years after treatment. He found that 2.1 per cent of patients irradiated for cervical carcinoma at the Me-

morial Hospital developed bladder sequelae. There has been only one of the treated patients in this series of stump cancers who has suffered any bladder injury, other than the development of fistulas as already mentioned. This patient had an advanced lesion and was in the group that received a minimum dose of 6 to 8 threshold erythemas in the primary lesion. This amount of radiation probably represents the upper margin of safety to normal tissues, when administered at the intensity, and over the time that these patients have been treated.

#### SUMMARY AND CONCLUSIONS

A series of 67 patients with carcinoma of the cervical stump were studied. There was reasonable evidence that in every patient the disease developed after supracervical hysterectomy had been performed. The low incidence of stump carcinoma does not justify risking the increased mortality of total hysterectomy instead of the subtotal operation, to prevent the later occurrence of cervix cancer in all patients from whom the uterine corpus is to be removed.

The patients were comparable in age, clinical extent of disease, histologic grouping, and symptomatology with all cases of cervix carcinoma. The five-year salvage of patients with stump cancer treated at least five years ago was 14 per cent, which is lower than the percentage survival of all patients with carcinoma of the cervix. The poor results may be attributed to insufficient irradiation, partially due to the difficulties encountered in making a correct application of radium in the absence of the uterine corpus. In most patients a single capsule of radium could be placed in the canal of the remaining cervix. However, in many cases the cervix had been destroyed by the disease, leaving an ulcerated crater in the vaginal vault. In the latter instance it was necessary to pack the radium against the lesion, which is less advantageous for treatment because of the poorer distribution of radiation resulting from such a faulty application. From an analysis of the treatment given the different patients, we may conclude that control of the primary lesion requires a minimum dose distribution of at least 6 to 8 threshold erythemas, when administered in the manner described. The five-year salvage of the patients with advanced disease who did receive this amount of radiation or more, as the minimum dose in the primary lesion, was 15 per cent. This result is comparable to that obtained in all patients with advanced cervix carcinoma in whom the uterus has not been removed for some preexisting surgical condition. If the primary lesion requires this dose, control of the parametrial disease, no doubt, necessitates at least an equal amount of radiation, which cannot be delivered by radium applied only to the cervix. The benefit obtained from only 2 threshold erythema doses delivered by external irradiation to the parametrial regions has been demonstrated.

By administering external radiation in small doses over a longer period of time, a greater total dose can be delivered to the parametria, than has been obtained in the past. Such a method, employing a different rate of administration than has been used in the treatment of stump carcinoma, may prove more effective in controlling the malignant disease in these regions. External irradiation can also be used to supplement the dose delivered to the primary lesion. By this means the inadequate treatment given to the cervix, because of the anatomical difficulties in making a satisfactory application of radium in some cases, may be overcome.

Patients who had already undergone a major surgical operation might be expected to report to their physician more promptly after the onset of unusual symptoms, than those who have had no previous illness. It is interesting to note that the patients in this series did not apply for medical aid any sooner than other cases of cervix carcinoma. The importance of medical education of the public cannot be overestimated in the control of cancer.

The authors wish to express their indebtedness to Mrs. Edith H. Quimby of the Department of Biophysics, without whose assistance it would have been impossible to carry on this work.

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The author observed that if a woman on whom an abdominal operation has recently been performed begins to menstruate, either at the time that corresponds to her regular period, or especially before her regular period, it is almost a certainty that the postoperative course will be smooth and uneventful. This sign seems to be so consistent and is so nearly infallible, that no matter how critically ill the patient may have been, or how serious the operative procedure was, as soon as this sign appears the author is relieved of further anxiety. If the flow appears the day after operation, and particularly if the appearance is before it is normally due, the convalescence will be especially uneventful, although its non-appearance does not necessarily indicate an unfavorable prognosis.

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## MATERNAL, FETAL, AND NEONATAL MORBIDITY AND MORTALITY\*

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IT IS difficult enough to analyze mortality statistics and secure accurate and comparable results. Statistics of morbidity are much more difficult to evaluate because the condition is poorly defined and there are very few comparable standards for different institutions and various communities. If anyone doubts the accuracy of this observation, then let him attempt to secure uniformity of opinion relative to such a simple standard as temperature as an index of febrile morbidity, or endeavor to obtain a generally accepted definition of puerperal infection.

In general, maternal morbidity and mortality statistics are undoubtedly more reliable than those pertaining to the fetus and newborn infant. It should always be remembered that no study of statistical reports can be more accurate than the original source. We all know how far death certificates fall short of absolute accuracy and, of course, all of our mortality statistics are based on death certificates. Naturally, the more careful study of patients before and after death tends to make the final statistical analysis more accurate. If such data are compared with those from other sources where less care is exercised, the results are not exactly comparable.

Furthermore, there are often more causes than one to which deaths may be attributed. In these cases, opinions may differ and rules may vary for the proper assignment of the primary cause. This is particularly true in various countries, not all of which have agreed to follow the same standards and rules. It is for this reason, among others, that there has been so much discussion relative to the exact position which the United States occupies with reference to maternal mortality in the family of nations.

Dr. Elizabeth Tandy has recently completed a report on "Comparability of the Maternal Mortality Rates of the United States and Certain Foreign Countries." The assembling of this material was begun by a Committee of the White House Conference on Child Health and Protection. This report is simply a study of the methods of assignment of maternal deaths as practiced in various countries. It has nothing to do with the study of the actual causes of maternal deaths. Sixteen countries made the assignment of these deaths from data appearing on

\*President's address before the Chicago Gynecological Society, June 22, 1934.

the death certificates sent to them. These assignments are believed to be indicative of present conditions and those which existed in 1927.

The mortality rates are not absolutely comparable for the various countries, but the methods of assignment in the United States correspond closely with those of Australia, Netherlands, New Zealand, and Scotland. The method now used in Denmark gives a higher rate, and the procedure employed in the other countries yields a lower rate than that of the United States. If one applies the rules of other countries the rate in the United States is lower, but a relatively high rate still remains which cannot be explained solely by variations in methods of assignment.

In most instances, the methods used in other countries lower our death rates from puerperal causes, but not sufficiently to remove the United States from its position near the top of the list of those having the highest maternal mortality rates.

It is still incumbent upon us to understand the cause for these high rates and to continue our efforts to reduce our casualties.

At first thought maternal and fetal morbidity and mortality would seem to be simply the sum total of the dire results of uncontrollable causes of the type of obstetric care rendered to individual patients. In a sense this is true, but on the other hand it must be recognized that there are great social and medical movements taking place, and over these the individual doctor and patient have relatively little control. Among these might be mentioned many changes which have taken place within the last fifty years and even a shorter lapse of time.

The increase in hospital beds has been enormous, followed by a tremendous increase in the hospitalization of maternity patients. Changed housing conditions have been a factor in bringing this about. There are now enough maternity beds in this country to accommodate practically all women having babies. They are not all ideal, but they exist, even though the institutions are not properly distributed geographically.

There has been much in favor of hospitalization of maternity cases from the points of view of both the patient and the physician. In many instances, the institutions were not properly planned and equipped for the adequate care of these patients. The personnel, both nurses and doctors, have too frequently had insufficient education and training in this field, as a rule through no fault of their own.

There has been much popular and medical propaganda for a quick and easy delivery at the expense of a safe one. This has led to the indiscriminate use of numerous analgesic and anesthetic agents and the frequent injudicious resort to operative procedures.

For many years past, a greater general interest in health problems and maternal and infant welfare, as well as other matters of vast social import, have led to more extensive individual and public interest in morbidity and mortality associated with maternity. There is no doubt



that in most countries health is a matter which is considered to be of increasing importance to both the individual and the community. Undoubtedly, on the one hand, the development of greater humanitarian ideals has been an important factor in producing these human interests. On the other hand, social conditions have arisen which have made the conservation of the health and lives of mothers and infants of greater importance to various states.

#### BIRTH RATE

Our mode of life and love of comfort and pleasure, together with economic and other social conditions, have generated a desire to limit the size of families, which is clearly shown in our rapidly diminishing birth rate and increasing number of abortions during the present century. Many of these conditions are not peculiar to this country, but are also met in many European countries.'

It is estimated that a birth rate of 16.6 per 1,000 persons is necessary to maintain a stationary population. This would necessitate about 3.4 children per family. The statistics relative to the birth rate in the United States prior to 1915, when the registration area was established, are not very accurate. At this time the rate was 25 per 1,000 population. Since 1915, the trend of the birth rate has been steadily downward to 17.3 in 1932. If this decline were projected into 1933 and 1934, the probable rate would be below that which would be required to stabilize the population.

It is obvious that if this decline continues there will be a gradual diminution in the growth of the population, at least in those countries which continue to have a diminishing number of births. If this becomes world-wide, it will mean a gradual reduction in the total population of the world. If the birth rate declines in some countries and some civilizations, and increases in others, it will mean an ultimate shift in national or racial domination. The same logic may be applied to groups within any given country, whether they are social, racial, or otherwise. In other words, within a more or less circumscribed community, the group with the highest birth rate and survival will ultimately dominate. Therefore, it becomes of great importance to races, nations, and various groups within nations to conserve the reproductive assets of the more desirable individuals. No one can determine which is the most desirable group or who the ultimate survivors will be. Various factors are responsible for the reduction in the birth rate, and it behooves us to consider the desirability of using some of these agencies to curtail the reproduction of individuals who are manifestly undesirable in any community.

The principal factor in the reduction of the birth rate is the rather general desire on the part of individuals to reduce the size of their families in order to cope more successfully with existing social and

economic conditions. This has been accomplished by various measures, such as contraception, sterilization, and abortions, which have steadily increased in number. It is impossible to know to what extent abortions have increased, but various authorities have estimated the number to be from one to every live birth to one of every two or three pregnancies.

It is not at all improbable that there are at least from 750,000 to 1,000,000 abortions in the United States each year. It is certain that maternal deaths from intentional abortions have tended to neutralize the decreased number of maternal deaths which have resulted from improved obstetric practice. It is apparent, therefore, that the desire to limit the size of families, even by measures so radical as the induction of abortion, leads not only to a diminishing birth rate, but also to an increased mortality rate, at least from this cause. The fetus, of course, is a total loss in these cases.

One result of the diminishing birth rate, causing a reduction in the size of families, is that a relatively greater number of women of low parity are delivered each year. In Chicago, during 1933, among 46,655 deliveries, the distribution of parity was as follows: Para i, 40.5 per cent; para ii, 26.9 per cent; and para iii, 14.2 per cent, making a total of over 80 per cent of all deliveries in the city among women with a parity of three or less. Approximately one-half of these women were delivered of their first child. There has been a percentage increase for first children born in the registration area. It was 27.3 per cent of the total number of births in 1917, and 31.9 per cent in 1931.

#### GENERAL CONSIDERATIONS

It is much easier to define mortality and obtain and analyze statistics pertaining to it than it is to define morbidity and secure accurate statistical analyses concerning it. As a rule, the same conditions and factors which in some cases produce morbidity may in other instances cause mortality. Morbidity may be defined as any condition which departs sufficiently from the normal to produce disability, no matter whether it is immediate or remote, temporary or permanent. Naturally, the degree of disability varies enormously, not only in its intensity but also in its duration. Without morbidity there would be no mortality.

The factors producing morbidity may or may not result in mortality. A fatality may occur close on the heels of the morbid condition, for example, in patients with acute hemorrhages, or death may result after a lapse of days as, for instance, in patients with infection or toxemia. The mortality may be a remote consequence of the primary condition and may occur years after the onset of the morbid state. Such a situation may present itself in vascular or renal diseases which were primarily associated with pregnancy.

Similar conditions exist with reference to the fetus and neonatal infant. Death may occur suddenly from an abnormal condition which causes a very transient morbidity, as in cases of abruptio placentae or prolapsus funis. A traumatic morbid state, as intracranial injury, may lead to rapid death, or the fetus may be born alive with more or less permanent damage, leading eventually to a long-continued disability and terminating ultimately in death.

A congenital condition may be present at birth and may result in a transient or long-continued morbidity and ultimately lead to death of the infant. A fetus may be born alive, apparently healthy, harboring a syphilitic infection which may lead to a protracted course of congenital syphilis, with ultimate handicapped survival or death. An infection, such as ophthalmia neonatorum, may develop in the newborn infant, producing a morbid state from which it may recover completely, or suffer partial or total blindness. An infection of the umbilicus may manifest itself subsequent to birth. This may be of minor consequence or of sufficient seriousness to cause a fatality.

There have been many improvements in maternity care and individual physicians and some institutions show very low morbidity and mortality rates. These good results have been counterbalanced by other factors which tend to and do actually neutralize the good results obtained in some areas.

It is well known that our negro population maintains a constantly high rate for both fetal and maternal morbidity and mortality. It should be clearly recognized that our hospitalization and coexistent operative incidence is unusually high and probably unequalled in any other country in the world.

#### OBSTETRIC MORTALITY AND MORBIDITY

Both the fetal morbidity and mortality are higher among women of lower parity, which is to say that the risk is greater in the first pregnancies than in subsequent ones, etc.

These are factors of great importance in maintaining obstetric mortality. A rather constant contributory factor is the more general and increasing use of various anesthetic agents, which tend to interfere with normal processes and facilitate, as well as necessitate, a greater incidence of operative deliveries. Another factor is the increased hospitalization of maternity patients, which adds to the safety and facility of operative obstetric procedures. No doubt, the marked increase in hospitalization of patients has resulted in an immoderate number of cesarean sections, which is an example of the increased major surgical intervention in obstetric cases. This statement also applies to increases in the number of other operations of lesser magnitude.

Whether or not the percentage of infections is increased by the hospitalization of patients is, to my mind, not a question of hospitalization or nonhospitalization, but one of the type of hospital into which maternity patients are brought and of the kind of obstetric care which is received.

Reference has already been made to the birth rates and maternal mortality rates. It may be of interest to cite the changes in the death rates over a period of years. The maternal mortality rate per 10,000 live births in the United States registration area has not been under 61 since 1915. It reached a peak of 92 in 1918, and was 63 in 1932. The urban rate has been consistently higher than the rural rate, and has not been under 64 since 1915, or less than 70 since 1917, with a peak of 96 in 1918, and a rate of 74 in 1932. The rural rate has not been below 55 since 1915. It reached a peak of 87 in 1918 and was 54 in 1932.

In Illinois, the general rate was lowest in 1930 and 1931, with a rate of 55. The peak was reached in 1929, with a rate of 68. The rate for 1932 was 56. There is some difference between the urban and rural rates. The lowest urban rate was 58 in 1931 and 1932, and the highest was 73 in 1929. The lowest rural rate was 40 in 1927, the highest was 57 in 1922 and 1929, while the rate in 1932 was 51.

There is a marked difference in the registration area between the maternal mortality in white and colored races, the latter being much higher. The rate for the colored race in 1915 was 106. The peak was reached in 1918, with a rate of 139, and the rate in 1932 was 98, which was the only year during which the 1915 rate was improved. The rate for the colored population in Illinois is considerably higher than for the white population, the maximum being 138 in 1923, and the minimum 65, which was in 1932.

The trend of infant mortality rates has been downward in the registration area since 1915. In 1932, the rates in Illinois per 1,000 live births were 48 in the state as a whole, 58 in urban communities, and 43 in the rural districts. There has been a gradual improvement in the neonatal mortality rate as shown by a constant decline from 44.4 in 1915, to 33.5 in 1932.

The major causes of maternal deaths may be divided into those which accompany or are incidental to the reproductive processes and those which are accidental to it. The former class of causes are grouped mainly under toxemias and traumatic conditions, no matter whether or not they are the result of spontaneous or operative deliveries, or hemorrhage. Most of the associated or accidental causes of maternal deaths may be grouped under such types of disease as infections of genital or extragenital origin, diseases of the cardiovascular-renal system, and pulmonary disease.

The major causes of fatality among the fetuses and the neonatal infants may be divided into those which affect the fetus and those which

destroy the newborn infant. The fetal period may be considered to extend through intrauterine life prior to labor, during parturition, and throughout the period following birth prior to the establishment of respiration, which is the real criterion for the termination of fetal life and the commencement of extrauterine life.

One may feel fully justified in classifying fetal deaths into (1) antenatal, including all fetal fatalities occurring during pregnancy prior to the onset of labor; (2) intranatal, consisting of all casualties during the process of labor, and (3) postnatal, taking place during the period intervening between the birth of the fetus and the establishment of its respiration.

Neonatal deaths are those which occur during the period following the establishment of respiration at birth and the end of the period during which the infant gradually adjusts itself to extrauterine life. This ordinarily requires about two weeks' time. Most of these fatalities are related to obstetric care. The majority of diseases and deaths of infants occurring later are not directly related to maternal care.

The causes of fetal and neonatal morbidity and mortality may be either of maternal, fetal, or extrauterine origin. The former includes all those morbid states which arise in the mother but affect the fetus. All conditions which arise from the germ cells and affect the fetus or fetal adnexa are to be considered as fetal in origin. It is recognized, however, that hereditary factors play a rôle in some of these conditions. In many others fetal and neonatal disorders result from faulty intrauterine or extrauterine environment.

It is difficult in many instances to make a clear-cut distinction between maternal and fetal causes. Hereditary and congenital conditions are responsible for many fetal and some neonatal deaths. Our present knowledge is not sufficient to prevent a development of these conditions. Many previable infants are born as the result of some maternal condition which leads either to intentional or unintentional premature labor. Careful prenatal care will prevent some of these previable and premature terminations of pregnancy.

Such infant fatalities may fit into any one of the varying classifications mentioned above. Our statistics include many deaths of previable infants because it is required that births be reported after a period of five months' gestation. The fetus, of course, does not attain viability until approximately the twenty-eighth week of gestation. Prematurity is an important cause of fetal and infant deaths, but our statistics include among premature infants many which should be classified as previable. The fatalities among premature infants are many because they are particularly susceptible to the etiologic factors which are responsible for the deaths of many infants born at term.

In addition to the general factors already mentioned as causing fetal and neonatal casualties, there are many specific causes for infant deaths

which may be grouped under the following: (1) Trauma affecting various structures and organs, chiefly those of the central nervous system; (2) infections, both acute and chronic, specific or nonspecific; (3) hemorrhages, traumatic or nontraumatic; (4) thermic causes, as refrigeration and insolation; and (5) faulty nutrition, etc.

Practically all of these causes mentioned as productive of mortality are also responsible for fetal and infant morbidity. We know very little relative to fetal morbidity during the antenatal period, although we have acquired some knowledge from the study of conditions which are carried over from this period into subsequent life, especially when fatalities occur. We know much concerning the morbidity of the intranatal period, and more concerning the neonatal period, although, on the whole, there are many gaps in our knowledge covering these special periods of life.

The morbidity may not manifest itself objectively or subjectively during the period when it is primarily acquired. The subsequent course of events reveals the morbid state which may be such as to eventuate in early death, or it may be carried along in an infant or child who is handicapped for a shorter or longer period of his life.

The prevention of the morbidity and mortality of mothers and infants cannot be absolute. The prophylaxis depends upon adequate care for the fetus and the mother, and for the infant from birth onward, which includes preconceptional, antepartum (antenatal), intrapartum (intranatal), postpartum (postnatal), gynecologic, and neonatal and infant care. Such care implies a properly educated laity who will seek and accept such attention, and personnel who are not only educated but also trained and experienced in administering it. Institutions and organizations are required and they must furnish the material, methods and personnel by which maternal and infant care can be supplied to all members of the community who require it.

It is undoubtedly unnecessary to point out that many individual physicians, nurses, etc., can furnish proper care to their own patients. It is, however, important to stress the fact that in many communities such work is not organized in a manner so that all mothers and babies can receive the requisite care either in their own homes or in the hospitals. The physicians of various communities can accomplish much if they will lead in organizing the resources of their own communities, so that adequate care will be available to all mothers and infants in their own localities.

With these general remarks, one may proceed to a consideration of the more specific causes of maternal, fetal, and infant morbidity and mortality.

Our statistics usually do not give a true picture of the course of events. In most cases, death is assigned more or less accurately to some

single cause. In many, and probably most, instances there are combined causes and with propriety the major one is charged with the result.

It is not desirable to fill your minds with statistics, but some presentation of information will give a rather definite idea of the relative importance of some of the many factors which contribute to these maternal and fetal casualties.

Statistics from various sources show that certain causes operate more or less uniformly and in about the same percentage and relative frequency in causing morbidity and mortality of mothers and their progeny. Some statistical facts stand out clearly in a recent report of the maternal mortality study conducted by the Children's Bureau. There were 7,380 maternal deaths analyzed. Over 1,550 of these women had not reached the seventh month, and one-third had not passed the third month of gestation at the time of death.

Some pertinent facts may be gleaned from this report. The mortality rate for colored women was nearly twice that for white women. About 9 per cent of these women had no medical care or received it only when moribund. Over 4,000 of these deaths occurred in hospitals, but the pregnancy was terminated in a hospital in only 2,600 of these cases. Relatively few of these patients had planned hospitalization. About 900 of these women who died during the last trimester had contemplated hospital deliveries. Seven per cent of these deaths occurred in unmarried women.

Over 5,600 of these women might have received prenatal care, but 54 per cent had no prenatal medical examination or care. Less than 1 per cent received adequate prenatal care. Only 13 per cent had good prenatal care, and over 75 per cent had poor, indifferent, or no prenatal attention.

The delivery care was often inadequate; emergency hospitalization was done in over one-half of the patients dying during the last trimester. Eighty-three per cent of these women were delivered by physicians, internes, or medical students, and 11 per cent by midwives. The doctors evaluated their own technic in this study and it was admittedly faulty in more than 50 per cent of the cases. It is interesting to note that more than one-half of these women had some operative procedure. In 37 per cent the operation was for delivery. Of those women who reached the last trimester, 45 per cent had attempted or completed operative deliveries. Details will not be given here, relative to the incidence of the various operative procedures, except to note that cesarean section was performed in 11 per cent of the women who reached the last trimester, and concerning whom information relative to operative procedure is available. Twenty-four per cent of all the operations for delivery were cesarean sections. Toxic states were the most frequent

indications for this operation. The most frequent causes of death in this group were puerperal albuminuria and convulsions, septicemia, and accidents of labor.

Abortions were defined for this report as previable terminations of pregnancy. Seventy-three per cent of the deaths following abortion were from septicemia and constituted 45 per cent of the total deaths from puerperal septicemia.

Puerperal septicemia was the most frequent cause of death and it accounted for 40 per cent of 7,380 deaths. In this series, 1,529 women died from sepsis in the last trimester and, of these, 94 per cent had a spontaneous onset and 65 per cent a spontaneous termination of labor. In 30 per cent of these women, toxemia was the chief or principal contributory cause of death. Twenty-six per cent of these deaths were due to puerperal albuminuria and convulsions. Only 12 per cent of these women had received good prenatal care, and over one-third of them were not seen by a physician prior to death, or were already in convulsions or coma when first seen. Hemorrhage caused 11 per cent of these deaths. Placenta previa, ablatio placentae, postpartum hemorrhage, and other puerperal hemorrhages are all listed. Traumatic conditions, as rupture of the uterus, inversion, etc., make up a small percentage of the total fatalities considered in this study.

There was no special study of fetal and neonatal deaths in connection with this analysis, but incidental data reveal that only 43 per cent of these women gave birth to living children, 8 per cent died undelivered, 29 per cent gave birth to nonviable fetuses, and 20 per cent were delivered of stillborn infants.

Munro Kerr has recently published a treatise dealing with maternal mortality and morbidity and the problems confronting medical practitioners in Great Britain. He recognizes, as do others in various countries, that the maternal mortality rate has remained stationary for years, and that the same etiologic factors continue year after year without material alteration, in spite of the fact that rates from other causes of mortality have been reduced. It is also believed the main reason for this failure to reduce mortality is not the lack of knowledge of measures to prevent these deaths, but neglect of application of known facts. This is evidenced by the observations that mortality is reduced materially where these well-known principles are practiced.

Statistics have been compiled for decennial periods, 1855 to 1930, for England, Wales, and Scotland. The maternal mortality rates for puerperal fever and other puerperal causes show no decrease in the last seventy-five years. It is interesting to note that the causes of mortality have the same order of incidence as was found in our country, viz., puerperal sepsis, eclampsia, hemorrhage, and other diseases and accidents of childbirth.



The percentage of frequency is not markedly different for the two countries, as Kerr gives approximately the following proportions for the causes just mentioned: Sepsis, 38 per cent; toxemias, 18 per cent; and hemorrhages, 12 to 15 per cent.

The outstanding causes of mortality are those mentioned above. Hemorrhage is not a great factor in the causation of resultant disability, the major causes of which are toxemia, infection, and trauma.

It is a curious fact that obstetric mortality has remained fairly constant not only for mothers but also for fetuses and neonatal infants. This is all the more striking when one realizes that other causes of death in women of the childbearing period have been markedly reduced, and that the later infant mortality rate is much less than it was thirty years ago.

The fetal death rate and the neonatal mortality rate have remained about the same for several decades in Great Britain. It is roughly estimated by these authors that congenital conditions cause some of the neonatal deaths, but that birth injury, infection and prematurity are each responsible for approximately 30 per cent of the neonatal deaths. They estimate the fetal death rate at about 185 per 1,000 conceptions.

The statistics from other sources show the same general trends, and it is unnecessary to repeat corroboratory evidence. It is important to call attention to the occurrence of deaths from conditions associated with pregnancy. The pregnancy often seriously complicates and aggravates these conditions, and if the mother does not die during pregnancy or soon after labor, her health may be impaired and her life shortened by a pregnancy complicating a condition in which cardiac, renal, or other vital function is seriously compromised.

One cannot take too myopic a view of maternal lives. It is hardly consistent to spare a life temporarily in the face of a pregnancy complicating a progressive condition which is made definitely worse by permitting the gestation to continue. Nor does it seem reasonable to expose a woman to the risks of repeated pregnancies in the face of a serious chronic or recurring disease.

There is evidence pointing to the conclusion that the first pregnancy is the most dangerous for the mother and the infant, the second and third are less hazardous, but that the fourth and subsequent pregnancies seem to become progressively more dangerous.

The causes of death and disability are quite well known. It is impossible to eliminate all maternal, fetal, and neonatal deaths. We know enough to prevent many of these fatalities. It is not so much the lack of knowledge as the failure to apply it generally which is responsible for the persistently high maternal and fetal morbidity and mortality rates.

## THE SYNTHESIS AND EXCRETION OF HIPPURIC ACID IN PREGNANCY

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THE present study was begun because it seemed that the metabolism of benzoic acid in the pregnant woman might be significant in relation to several physiologic functions which may be disturbed in the presence of a fetus and which have hitherto received inadequate attention.

Hippuric acid is present in normal human urine in varying small amounts as the end-product of the detoxification of benzoic acid and benzoates derived from foodstuffs and the splitting of aromatic compounds in the intestine. The conjugation of benzoic acid with glycine to form hippuric acid is typical of the mechanism by which the body takes care of a certain group of related toxins. In man it is felt certain that the conjugation occurs in the kidneys and liver and perhaps other tissues. If it be assumed that the tissues are capable of the synthesis, then the formation of hippuric acid from a given quantity of benzoic acid depends upon the availability of an equivalent quantity of glycine. Since there is but a small amount of the latter circulating and free in the tissues,<sup>1</sup> it, in turn, must be synthesized if much is demanded and none ingested. It seems definite that this synthesis occurs for the most part in the liver. From this fact Quick<sup>2</sup> has evolved a test of liver function which consists of the quantitative determination of hippuric acid eliminated after the ingestion of a definite amount of sodium benzoate and the comparison of the findings with the expected rate which is constant in normal individuals. The recovery of hippuric acid has so far been found to be low in catarrhal jaundice, hepatitis, syphilitic cirrhosis, and prolonged obstructive jaundice, but may be normal in Laennec's cirrhosis.

Our knowledge of hepatic pathology as found postmortem in the toxemias of pregnancy is complete enough, yet there has been but inconclusive information elicited concerning the development of the functional disturbances of liver physiology which may be of primary importance. Nearly all available tests of liver function have been tried in cases of normal and toxemic pregnancy. These include the phenoltetrachlorophthalein, bromsulphalein, Widal's hemoclastic crisis, Ehrlich, Schlessinger, Fouchet, van den Bergh, nitrogen partition, and levulose tolerance tests. The results have been reviewed by Stande and by Cross.<sup>4</sup> There is a general agreement that the findings a

negative in normal cases. The Widal, Ehrlich, Schlessinger, Fouchet, and levulose tolerance tests give unreliable results.

In the toxemias the excretion of the dyes is often delayed, but it is not possible thereby to distinguish between nephritic and eclamptic toxemia. Bilirubinemia as indicated by the van den Bergh reaction when found indicates definite liver damage.

Sullivan, Tew, and Watson<sup>5</sup> have recently reported a series of 80 cases of both normal and toxemic pregnancy on whom determinations were made of the excretion rate of intravenously administered bilirubin. They reviewed similar tests performed previously by Kaufman, Stroebe, Hofbauer, Soffer, and Watson. In general agreement with these others, they found that during the first half of normal pregnancy liver function by this test is unimpaired, but that in the second half evidence of disturbed function can be demonstrated in at least 30 per cent of the cases. Toxic patients with definite signs of renal insufficiency tend to show less retention of injected bilirubin than those with normal kidney function.

It was indicated that the impairment of liver function occurring in both normal and toxic pregnancies is of a temporary nature, since the bilirubin excretion test tends to return to normal following the termination of pregnancy. This test is the only one thus far tried which gives fairly positive indication of disturbed hepatic function in normal pregnancy.

From the foregoing it is apparent that any new approach to an understanding of liver function in pregnancy is worthy of trial.

#### METHOD

One hour after a light breakfast, from which fruit is excluded, the patient voids and is then given 5.9 gm. of sodium benzoate (the equivalent of 5 gm. benzoic acid) and half a glass of water. The benzoate is conveniently administered as 30 c.c. of a 19.7 per cent solution to which some peppermint water is added to disguise the taste. No further fluids are allowed until the test is completed. Urine is collected at one-hour intervals for four hours. If the urine is not to be treated in a short time it must be preserved with toluol to prevent hydrolysis of the hippuric acid which readily occurs, especially in alkaline urines. For the determination of the hippuric acid the simplified Method I of Quick<sup>2</sup> was used in this study. Urines containing show, lochia, or albumin must be acidified with acetic acid, boiled, and filtered before further treatment or the final filtration will be much delayed. Specimens with a volume of more than 100 c.c. are acidified with acetic acid and reduced to about 50 c.c. by boiling or evaporation. One cubic centimeter of concentrated HCl is added to each specimen. If this does not produce a reaction acid to Congo red, a generously sufficient further quantity of acid is supplied. The urine is stirred vigorously until precipitation of the hippuric acid is complete, then is allowed to stand for an hour, whereafter the precipitate is collected by filtration. For the filtration it is most convenient to use a filter flask carrying an ordinary 60° glass funnel with a 25 mm. Hirsh filter plate and 4.25 cm. Whatman No. 2 paper. The hippuric acid is allowed to dry in warm air and weighed to the second decimal place. There is so little variation in the filter papers that one can be used for a counter-balance. The filtrate is measured and the amount of hippuric acid remaining in solution calculated by multiplying the volume in cubic centimeters by 0.0023. This added to the weight of the precipitate gives the total hippuric acid recovered in one hour. In order to have a uniform basis of comparison, the hippuric acid is then represented as benzoic acid by multiplying by 0.68.

The average total normal excretion for four hours has been found to be 3 gm. of benzoic acid, hence the total is divided by 3 to get the percentage of average normal. It is also found that the maximum in one hour, usually the second or third, should be about 0.9 gm. or more. The output varies somewhat in relation to the size (the surface area) of the individual and a 90 per cent recovery is to be considered normal for a small subject. Occasionally a test showing a subnormal total output is interpreted as normal when the output for one hour is found to be 0.9 gm. or more. Such interpolation is made necessary by the possibility of delayed absorption of sodium benzoate, though assimilation is normally rapid.

Another possible explanation of a low recovery of hippuric acid than the failure of synthesis must receive consideration, namely, that the kidneys may be unable to excrete it when it has to be formed. This question is particularly likely to arise in the toxemias of pregnancy with hypertension and albuminuria. Quick<sup>2</sup> states that hippuric acid behaves like other nitrogenous excretory products and that when there is nitrogen retention it too will be retained. The exact state of the kidney threshold to hippuric acid and its variation in kidney dysfunction remains to be determined. It was first thought that patients showing a subnormal excretion of hippuric acid after sodium benzoate could be checked by giving an equivalent quantity (7.33 gm.) of hippuric acid by mouth after conversion to sodium hippurate. This was tried and found not entirely satisfactory. It has been demonstrated that the absorption of sodium hippurate in the rabbit is much slower than of sodium benzoate<sup>6</sup> and this is apparently also true for man, since after sodium hippurate by mouth the hourly excretion of the hippuric acid is often irregular and even in normal individuals the total hippuric acid excreted in four hours is often less than after an equivalent amount of sodium benzoate. After some indeterminate checks by the oral administration of sodium hippurate, it was decided that only by giving it intravenously could its excretion be definitely determined. This has been done without ill effect in animals. Swick<sup>7</sup> has found it is feasible to give intravenously for pyelography 10 to 20 gm. of sodium ortho-iodohippurate in 40 per cent solution. This salt is, of course, closely related to the unsubstituted sodium hippurate. He observed that there was a very sharp curve of excretion, 60 to 66 per cent being recovered in the first hour and 70 to 80 per cent in two hours. After a sterile preparation of sodium hippurate, neutral to phenolphthalein, representing 20 per cent of hippuric acid was tried intravenously on myself and my colleagues without untoward reaction, it was used as a check on some patients. Ten cubic centimeters representing 2 gm. of hippuric acid were given at a time, injecting slowly. Occasionally a transient feeling of warmth and flushing without significant change in the pulse rate appeared at the conclusion of the injection. Urines were first collected at one-half, one, and two hours after the injection. In a short series of normal individuals tested it was found that an average of 64 per cent was excreted in the first half hour, an additional 14 per cent at the end of an hour, and only 8 per cent more after the lapse of the second hour. Hence it is felt that any delay in the first thirty minutes and a low total for one hour represents a diminished renal capacity for the excretion of hippuric acid. Kingsbury and Swanson,<sup>8</sup> Bryan,<sup>9</sup> and Morgulis, Pratt, and Jahr<sup>10</sup> have investigated the excretion of hippuric acid as a test of renal function on the premise that the synthesis occurs in the kidney. The conjugation of benzoic acid in man is probably not limited to the kidney. It is likely that the excretory mechanism of the kidney behaves in relation to hippuric acid much as it does to other nitrogenous metabolites. The above investigators gave sodium benzoate by mouth equivalent to 2 gm. of benzoic acid and calculated the percentage of benzoic acid recovered from the urine at two and three hours in the first two investigations, and at six and twenty-four hours in the last. Kingsbury

TABLE I. EXCRETION OF HIPPURIC ACID AFTER SODIUM BENZOATE AND SODIUM HIPPURATE BY MOUTH

CASE	HOSP. NO.	AGE	PARITY	WEIGHT LBS.	GESTA- TION	HOURLY OUTPUT OF HIPPURIC ACID AS GRAMS OF BENZOIC ACID					% NORMAL	REMARKS	TENTATIVE DIAGNOSIS
						1	2	3	4	TOTAL			
1	#15110	25	i	168	Term + 11	0.2 0.54	0.53 0.81	0.22 1.01	0.91 0.77	1.86 3.13	62 104	? Irregular absorption in 1st test. Nephrectomy 1930 tendency to hyper- tension with intermittent rise of B.P. At term 140/100 falling to normal postpartum: B. U. N. 12. Uric acid 4.	Low reserve kidney.
2	M. G. (O. P. D.)	28	ii	230	-160	0.40	1.14	1.07	0.48	3.09	103		Normal
3	G. C. (O. P. D.)	22	i	145	-162	0.56	0.68	0.99	0.41	2.64	88		Normal
4	#15160	18	i	140	- 17 + 10	0.25 0.82	0.61 0.72	0.67 0.84	Lost 0.72	3.10	103	Intermittent hyperten- sion late in pregnancy. At term 150/100. Al- buminuria ++ 4th speci- men lost in 1st test. Test nevertheless subnormal.	Low reserve kidney.
5	#15118	21	i	130	Term + 11	0.35 0.18	0.50 0.33	0.59 0.43	0.88 0.90	2.32 1.84	77 61	Urine in 2nd test stood with- out preservative. Hydrol- ysis likely.	Normal.
6	M. J. (O. P. D.)	32	i	165	- 76	0.22	0.75	0.75	0.54	2.26	75		Normal.
7	#15125	28	ii	124	- 1 Term* + 10	0.24 1.00 0.71	0.27 0.55 1.37	0.98 0.82 0.62	0.86 0.48 0.45	2.35 2.85 3.15	78 95 105	*7.3 gm. hippuric acid by mouth.	Normal.

Unless otherwise indicated, figures are results after 5.9 gm. sodium benzoate by mouth.

In the sixth column the figures designated minus (-) give the number of days before calculated term or delivery, plus (+) the number of days postpartum.



TABLE I—CONT'D

CASE	HOSP. NO.	AGE	PARITY	WEIGHT LBS.	GESTA- TION	HOURLY OUTPUT OF HIPPURIC ACID AS GRAMS OF BENZOIC ACID					% NORMAL	REMARKS	TENTATIVE DIAGNOSIS
						1	2	3	4	TOTAL			
15	#15141	23	ii	130	-184 -178	0.46 0.37	0.45 0.77	0.75 0.67	0.48 0.67	2.14 2.48	71 83	Vomiting 8 weeks. Icteric index 40. B. U. N. 36. Uric acid 9 on admission falling to normal shortly. Icteric index 5 on day of first test.	Hyperemesis gravidarum.
16	R. L. (O. P. D.)	20	i	120	-200	0.18	0.95	0.90	0.86	2.89	96		Normal.
17	#15197	29	ii	165	- 7	0.66	0.96	1.18	0.58	3.38	112	Slight hypertension since 5th month 132/70 to 142/90. At term 148/80. Occasional faint trace of albumin.	Low reserve kidney.
18	#15172	23	i	148	- 8 + 10	0.24 0.67	0.96 0.96	0.71 1.09	0.35 0.92	2.46 3.54	82 115	One transient rise in B. P. to 138/100. No albuminuria.	Low reserve kidney.
19	#15182	31	i		Term	0.14	0.60	0.66	0.40	1.80	60	B. P. 140/90 albumin + last three weeks. B. U. N. 15. Uric acid 4.2.	Low reserve kidney.
20	#15078	34	viii	174	- 6 + 9	0.18 0.59	0.73 0.92	1.07	0.43 0.88	1.34 3.46	45 115	Systolic hypertension with faint trace of albumin since first seen in 5th month. B. P. at term 132/90. Stillbirth. Cord and placenta show syphilitic histology. Maternal Wassermann negative.	Chronic nephritis. ? Syphilis

TABLE I—CONT'D

TABLE I—CONT'D													
	#15205	29	i	151	Term + 10	0.41 1.09	0.76 1.77	0.60 1.09	0.82 0.12	2.59 4.07	86 138	Trace albumin 1 week before term, B.P. normal. On admission B.P. 178/98. Albumin ++, sl. edema, no symptoms. B.P. labile but returned to normal postpartum.	Pre-eclamptic toxemia.
22	#16333	31	iii	148	+ 2 + 11	0.37 0.60	0.85 1.07	0.29 1.09	0.94 0.77	2.65 3.53	88 114	Previous deliveries antepartum course normal. Postpartum B.P. 164/100, moderate headache, albumin slightest possible trace. B.U.N. 21. Uric acid 6.3. B.P. fell to normal by fifth day.	Postpartum. Pre-eclamptic toxemia.
23	#15206	22	i	163	- 2 + 10	0.41 0.32	0.72 1.16	0.46 1.22	0.17 Lost	1.76	59	Slight albuminuria without hypertension since 7th month. B.P. postpartum 132/100 falling to normal by tenth day. Fourth specimen lost in second test, but return obviously normal.	Low reserve kidney.
24	#2182A	42	v	160	- 39	0.27	0.62	0.50	2.76	92	Previous deliveries normal except for occasional slight albuminuria. Hypertension and albuminuria since seventh month. B.P. 140/90 to 168/100.	Chronic nephritis.	



and Swanson, and Bryan considered a recovery of 70 per cent in two hours, and 85 to 90 per cent in three hours as normal, and found the recovery diminished in certain cases with kidney dysfunction.

Bryan tested 12 normal pregnant and puerperal women with normal results, 12 cases which were considered abnormal on the basis of a past history of scarlatina, tonsillitis, or rheumatism were found to have diminished two-hour phenolsulphonephthalein tests, averaging 44 per cent and benzoic acid recovery of 49 per cent at the second hour and a total of 76 per cent at the third. One patient had "toxemia," one puerperal fever. No other clinical findings are given. Morgulis, Pratt, and Jahr based part of their interpretation on the recovery of free benzoic acid, and Bryan considered the presence of as much as 3 per cent free benzoic acid as an index of hepatic dysfunction. It is more probable that the free benzoic acid was the result of the hydrolysis of hippuric acid, and perhaps of small quantities of glycuronic acid monobenzoate in standing urine, which readily occurs if the urine is not treated with preservatives or analyzed at once.

Because these workers used both a different quantity of benzoate and a different analytical method, it is not possible to draw a close comparison between their results and those presented herein. I feel, in addition, that the state of renal function in their patients cannot be unequivocally designated by the two-hour excretion of phenolsulphonephthalein alone as a control. It does seem possible to conclude that a diminished excretion of hippuric acid can be anticipated when renal function is depressed.

#### RESULTS

Forty-nine tests were done on 24 patients. The results are summarized in Table I. Only one case of the 15 patients tested at or near term showed an entirely normal total 4-hour excretion of hippuric acid after sodium benzoate. Five of these patients had in a single hour a normal output of 0.9 gm. or more. Four cases were normal pregnancies by all clinical criteria, the rest of the patients had varying degrees of toxemia as noted in Table I. The average output of hippuric acid was somewhat higher in the normal than in the toxic cases, 79 per cent against 69 per cent respectively. The patients with particularly low output were toxic, yet the one patient at term with a normal output (No. 17) had a mild toxemia. Of those patients on whom a repeat test was obtained on the tenth day postpartum only one had a subnormal return, and it is possible that in this case there was an error in technic, since the analysis was delayed and the urine stood without preservative.

Three patients who were given 7.3 gm. of neutralized hippuric acid by mouth (Nos. 7, 12, and 13) showed a low normal recovery of hippuric acid whereas their output after sodium benzoate was slightly subnormal.

Six of the patients at term were given 2 gm. of hippuric acid as the sodium salt intravenously (Nos. 13, 18, 20, 21, 22, and 23). Four showed rather marked depression of excretion, particularly in the first half hour. One on whom a repeat test was done on the tenth day postpartum (No. 23) showed some improvement but still considerably delayed excretion, although a fifteen-minute fractional phenolsulphonephthalein test done the same day was normal. The two patients who had a normal or but slightly depressed excretion (Nos. 21 and 22) had toxemias developing very late in pregnancy tentatively classified as preeclampsia.

Six tests were done on normal women in the fourth to eighth month of pregnancy. One of these (No. 3) had a slightly low but essentially normal output, another (No. 6) showed a definitely low recovery, the rest were entirely normal. One patient (No. 24) with a tentative diagnosis of chronic nephritis had at the end of the eighth month a low output of intravenous sodium hippurate, but a normal output of hippuric acid after sodium benzoate by mouth.

A patient with severe vomiting and moderate icterus in the third month of gestation (No. 15) showed a definitely impaired synthesis of hippuric acid in a test done after her icteric index was normal, while another test a week later showed improvement.

With the exception of occasional vertigo no untoward reactions occurred from the sodium benzoate. There was no vomiting, though it is unlikely that patients with nausea would be able to tolerate the test until they are able to retain food.

TABLE II. EXCRETION OF HIPPURIC ACID AFTER INTRAVENOUS SODIUM HIPPURATE

CASE	DAY	ONE-HALF HOUR	ONE HOUR	TWO HOURS
13	+ 8	69%	79%	83%
18	- 2	38%	53%	61%
20	- 6	30%	63%	75%
21	+ 1	61%	79%	
22	+ 2	51%	77%	
23	- 1	6%	29%	
	+10	26%	62%	
24	-34	11%	31%	

#### DISCUSSION

While it is not possible from the information provided to date by this investigation to define the exact status of the synthesis of hippuric acid in pregnancy, nor at present to separate the nephric and hepatic factors, it seems likely that as the majority of women reach term there is a definite disturbance of the excretion of hippuric acid which does not persist through the puerperium. The distinction between the normal and toxic patient's metabolism of benzoic acid is, again, not plain, but in this series the recovery of hippuric acid has been somewhat less in the latter.

A most interesting field of speculation is opened by a consideration of the detoxification and excretion of the aromatic substances, of which benzoic acid is a type.

The nature of the hypothetical toxins that disturb pregnancy is unknown. It is known that toxic aromatic substances occur in the body, for example, as a result of intestinal hydrolysis. If it were possible to demonstrate a failure of the normal mechanisms of detoxification either through a deficiency of the substance, in this instance, glycine, necessary to conjugation (perhaps secondary to hepatic dysfunction) or a depression of renal excretion, another point for attacking the problem would be provided.

One of the more constant chemical findings in the most characteristic of the toxemias of pregnancy, eclampsia, is an elevated blood uric acid. It has long been considered that uricidemia was one of the first evidences of renal deficiency, preceding the retention of other nitrogenous substances. It is now recognized that this is very doubtful.<sup>11, 12</sup> Quick<sup>12</sup> points out that uric acid excretion tends to be constant but definitely influenced by certain metabolic and toxic materials. Its excretion is increased by substances he designates as anti-ketogenic, e.g., glucose, glycerol, pyruvic acid, glycine, alanine, aspartic and glutamic acids, and by a high protein diet. Excretion is diminished by ketogenic substances: a high fat diet, fasting, acetoacetic acid by mouth, by lactic acid either administered or produced in excess metabolically, and by benzoic, phenylacetic and other aromatic acids. It has been shown already that an increase in lactic acid occurs in eclampsia. It is also suggested that toxins similar to these aromatic acids may be responsible for the decreased elimination of uric acid. Another possibility is the diversion of the amino acids or other anti-ketogenic substance to the fetus.

If the conjugative mechanism should prove to be still adequate, in the presence of a deficiency of the substance with which the toxin is conjugated, for example, glycine, it may be possible to make a therapeutic replacement. Glycine, for one, is readily available as such and is present in high percentage in gelatin. Such substances also may accelerate the excretion of already conjugated aromatic compounds.<sup>13, 14</sup> It is also worthy of consideration that the low protein dietary treatment of toxemia may, in fact, lead to a deficient intake of these elements, and place a burden on the mechanism of synthesis.

It is felt that a further study of the metabolism of benzoic acid in pregnancy including a more definite determination of the renal threshold of hippuric acid, a parallel study of the blood and urine uric acid levels, and a trial of the effect of high glycine feeding would be profitable.

#### SUMMARY

1. It is shown that the excretion of hippuric acid after the administration of sodium benzoate is diminished toward the termination of normal and toxemic pregnancies. In some cases there is depressed excretion of sodium hippurate given intravenously.

2. A case of hyperemesis gravidarum showed definite liver dysfunction by this test.

3. The possible relation of the conjugation and excretion of aromatic toxins to uric acid excretion and the toxemias of pregnancy is discussed.

I am indebted to Dr. Armand J. Quick for invaluable technical advice and criticism.  
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## A STUDY OF BLOOD SUGAR LEVELS IN ECLAMPSIA

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IN RECENT articles on the treatment of eclampsia there appears an increasing use of dextrose in the treatment of pregnancy toxicosis. There still exists, however, some controversy on the rationale of this therapeutic procedure. Various methods of administration and doses

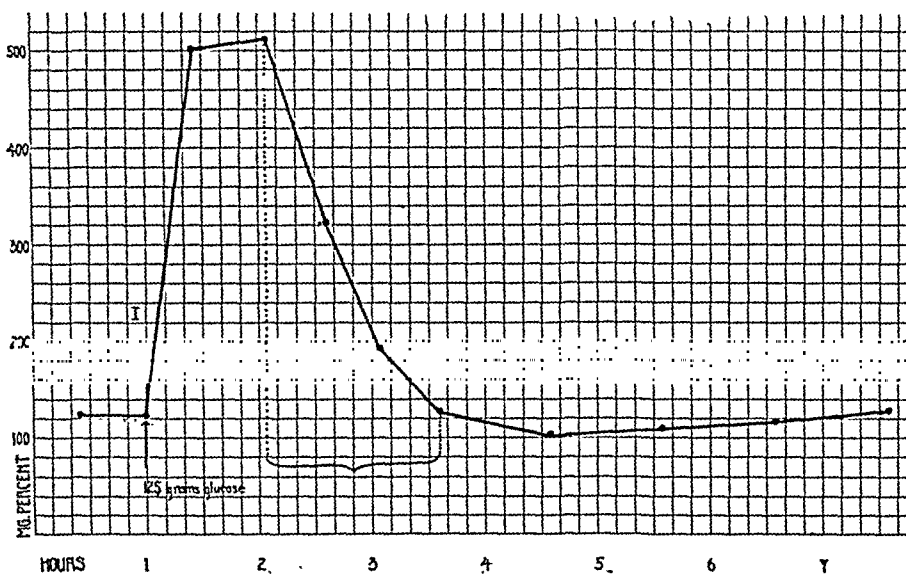


Fig. 1.—Case 1. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	1 hr. 30 min.	258.0 mg. per hr.	—	—

have been recommended based upon a variety of theories regarding the beneficial effects of dextrose infusions. For this reason we have studied the influence of blood sugar concentration on the incidence of convulsive manifestation of eclampsia.

We have favored the use of dextrose in the treatment of our eclamptic patients for its protective influence against liver degeneration and the strong diuretic effect it produces. The diuretic efficiency of dex-

trose must be directly proportional to the molecular concentration that it reaches in the circulating blood and the duration of time that is held at this given high level.

In the selection of cases for this study only those patients which showed convulsive manifestations of eclampsia, immediately preceding the period of observation were employed. Medication, other than

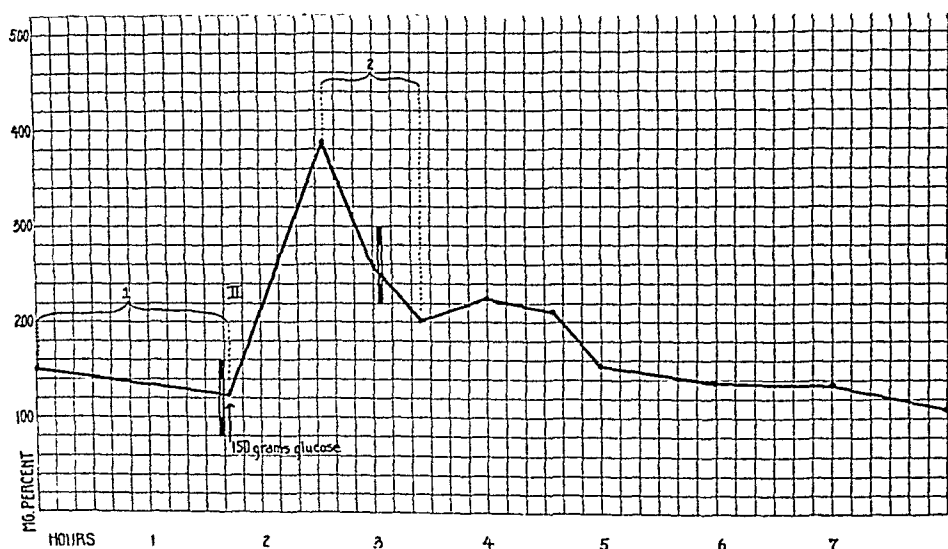


Fig. 2.—Case 2. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	1 hr. 43 min.	21.5 mg. per hr.	1	at 122 mg. %
2	50 min.	222.0 mg. per hr.	1	at 250 mg. %

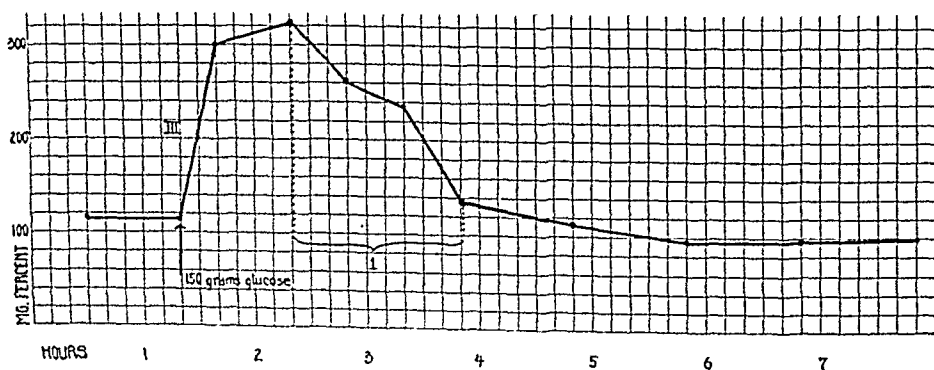


Fig. 3.—Case 3. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	1 hr. 30 min.	124.0 mg. per hr.	—	—

insulin and glucose, was not administered during the experimental period except in three cases, a notation of which is made in the case report.

During the earlier studies (Cases 1, 2, 3, 4, and 6) the blood sugar determinations were made upon capillary blood from the finger tips by the method of Folin and Malmros.<sup>1</sup> In the remainder of the series blood was obtained from the median vein and preserved in tubes containing oxalate and fluoride<sup>2</sup> in the ice box until analyzed eight or ten hours afterward at the latest. The blood proteins were precipitated according to Somogyi<sup>3</sup> and the sugar determined by the method of Folin.<sup>4</sup>

## RESULTS

In Table I is presented the blood sugar concentrations at the beginning of the study. Our data are presented in Figs. 1 to 14. Analysis of these charts may be found in Table II.

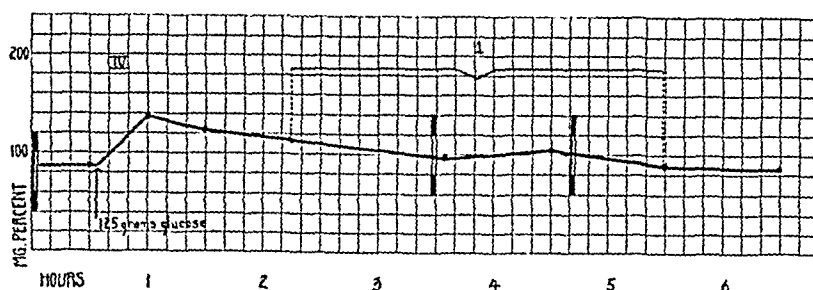


Fig. 4.—Case 4. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	3 hr. 15 min.	8.5 mg. per hr.	2	at 100 mg. %

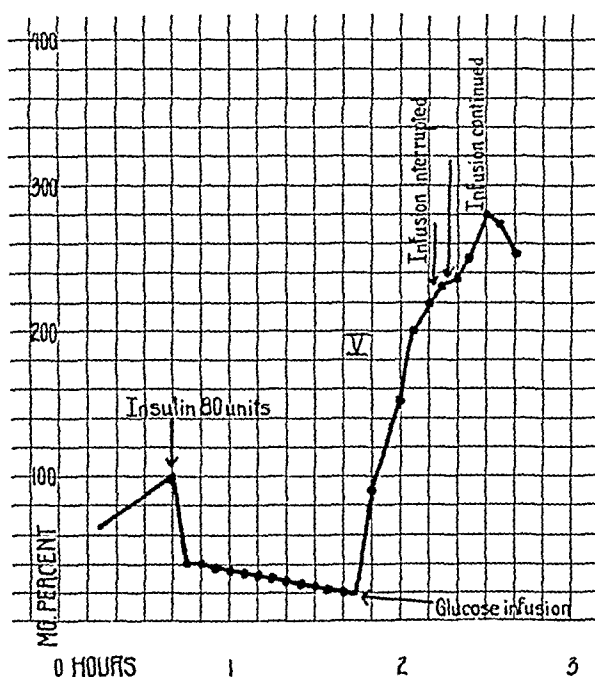


Fig. 5.—Case 5. Samples taken at five-minute intervals. After initial drop curve is smooth with no abrupt changes until glucose infusion was interrupted for a few moments and until peak was reached.

## DISCUSSION

In the analysis of our material we find that due to the rapid administration of dextrose most of our time was spent in the study of blood sugar values during their declining periods. It is, therefore, probable that irrespective of the effect of increasing and decreasing blood sugar levels on the incidence of convulsions, the mathematical possibility of convulsions occurring during the declining periods of our graphs is greatly increased over the possibility of their occurrence during increasing glycaemic levels.

TABLE I. GLYCEMIC LEVEL ON ADMISSION

HYPO	NORMAL	HYPER	
89	105	125	
	116	121	
1	2	2	Av. 111.2
Folin-Wu Normal—90-120			
69	96		
64	93	395	
	72	273	
	78	148	
2	4	3	Av. 142.9
Somogyi-Folin Normal—70-100			

TABLE II. AVERAGE RATE OF FALL IN BLOOD SUGAR CONCENTRATION AND INCIDENCE OF CONVULSIONS.

	AVERAGE RATES OF FALL	NO. OF CONVULSIONS	SUGAR CONC. MG. %
Group I. Receiving no insulin.			
Case 1	258.0	—	—
Case 2	21.5	1	112
	222.0	1	250
Case 3	124.0	—	—
Case 4	8.5	2	100
Group II. Receiving insulin			
Case 5	—	—	—
Case 6	225.0	1	170
	50.0	1	110
Case 7	40.0	1	250
	188.0	—	—
	40.0	1	120
Case 8	0.0	1	93
	39.0	1	34
<i>Rise</i>	1098.0	—	—
	140.0	—	—
Case 9	0.0	1	148
	20.0	1	57
Case 10	204.0	—	—
Case 11	26.0	—	—
	6.0	—	—
<i>Rise</i>	384.0	—	—
	313.0	1	470
	64.0	1	330
	64.0	1	265
Case 12	200.0	—	—
	9.0	2	202
<i>Rise</i>	810.0	—	—
	188.0	1	700
Case 13	188.0	1	690
<i>Rise</i>	29.0	1	93
	52.0	1	93
<i>Rise</i>	137.0	1	382
<i>Rise</i>	112.0	1	340
Case 14	0.0	1	96
	24.0	1	90
	15.5	1	65
<i>Rise</i>	314.0	1	580
<i>Rise</i>	64.0	1	678
	46.0	1	636

In that the occurrence of convulsions has been suggested to be due to a relative hypoglycemia, that is, a rapid fall in blood sugar level from a preexisting higher level to a lower level, regardless of the

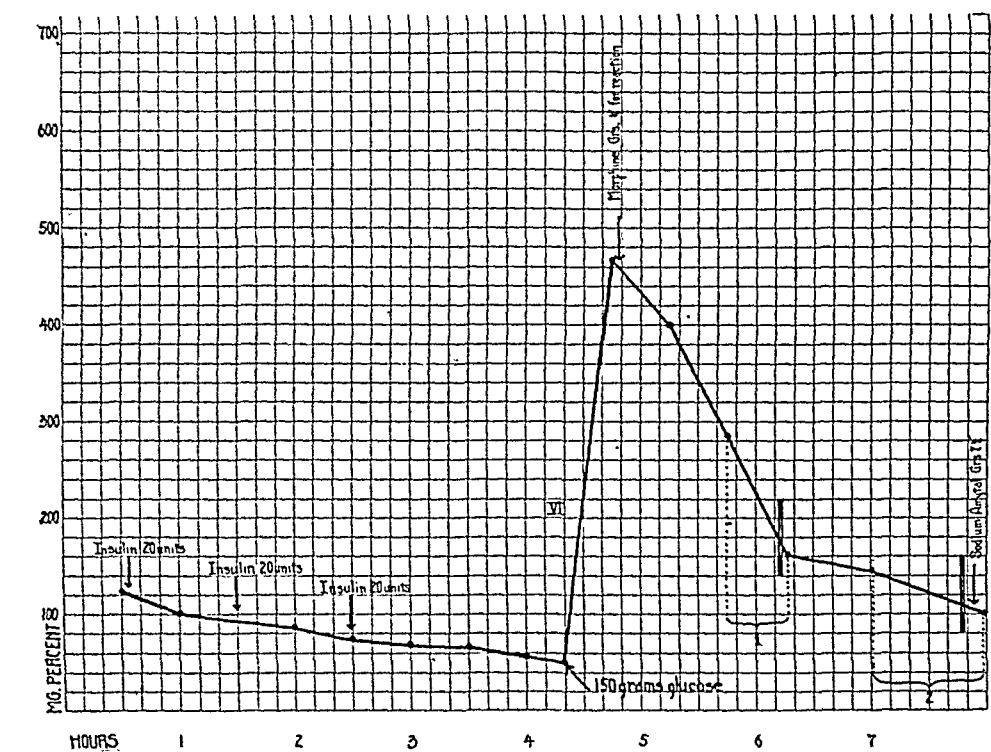


Fig. 6.—Case 6. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	33 min.	225.0 mg. per hr.	1	at 170 mg. %
2	1 hr.	50.0 mg. per hr.	1	at 110 mg. %

(Medication—Morphine and sodium amytal)

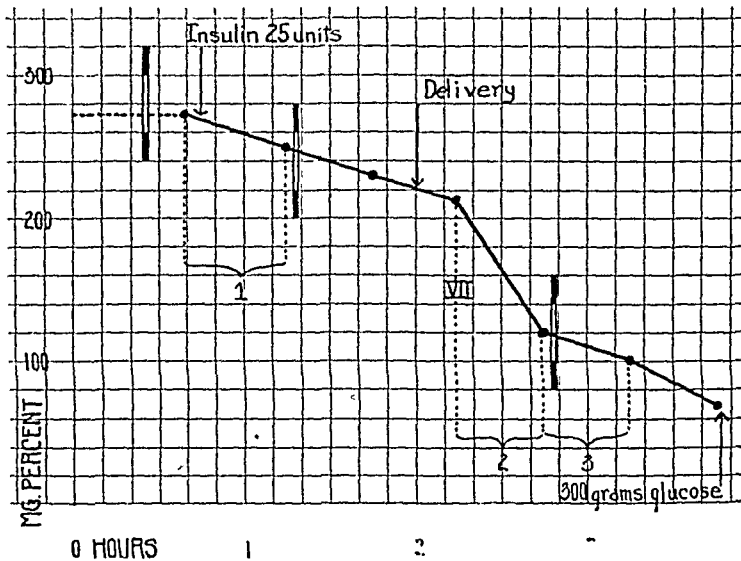


Fig. 7.—Case 7. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	35 min.	40.0 mg. per hr.	1	at 250 mg. %
2	30 min.	188.0 mg. per hr.		
3	30 min.	40.0 mg. per hr.	1	at 120 mg. %



absolute level, we have first selected a series of four cases which exhibited convulsive manifestations of eclampsia immediately preceding the study in which we gave rapid infusion of large doses of dextrose.

In Cases 1 and 3 it may be seen that no convulsions occurred during the decline in blood sugar concentration. Case 1 is especially convincing because of the rapid

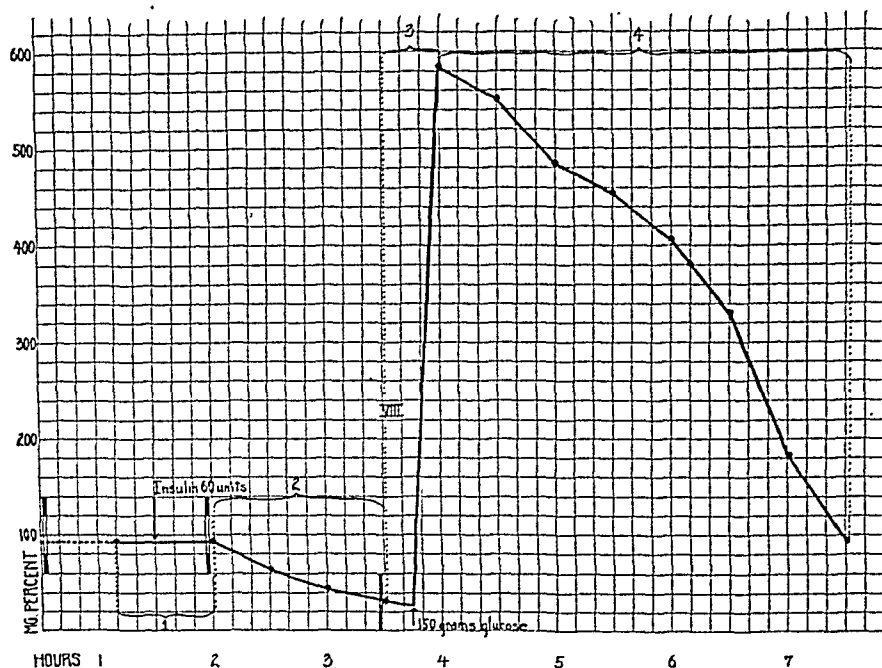


Fig. 8.—Case 8. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	50 min.	0.0 mg. per hr.	1	at 93 mg. %
2	1 hr. 30 min.	39.0 mg. per hr.	1	at 34 mg. %
	30 min.	Rise of 1098 per hr.	—	—
	3 hr. 30 min.	140.0 mg. per hr.	—	—

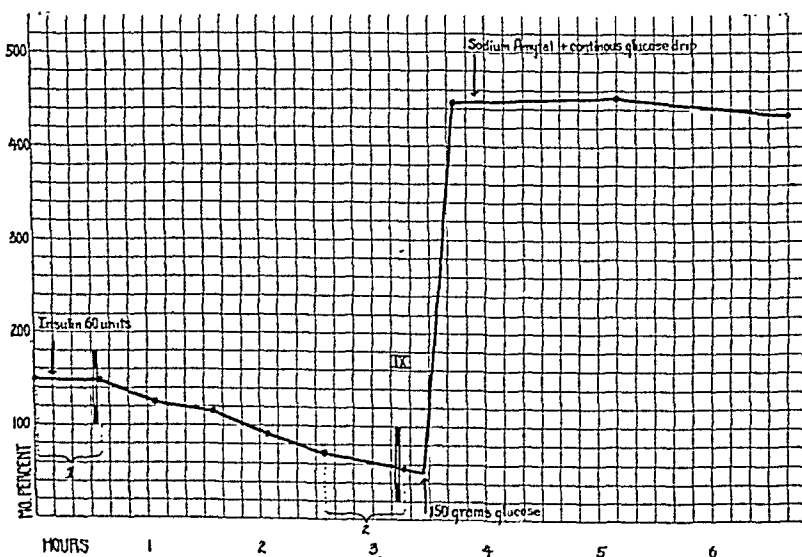


Fig. 9.—Case 9. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	35 min.	0 mg. per hr.	1	at 148 mg. %
2	43 min.	20 mg. per hr. (Sodium amytal)	1	at 57 mg. %

decline in blood sugar value to a relatively subnormal value. In Case 2 the incidence of convulsions was not increased in proportion to the rapidity of decline in blood sugar levels. In Case 3 although there was a slower rate of decline in blood sugar, the incidence of convulsions was greater than in Case 2.

A study of the remaining charts shows, as summarized in Table II, that there is no relationship between the incidence of convulsions and the rapidity in which rela-

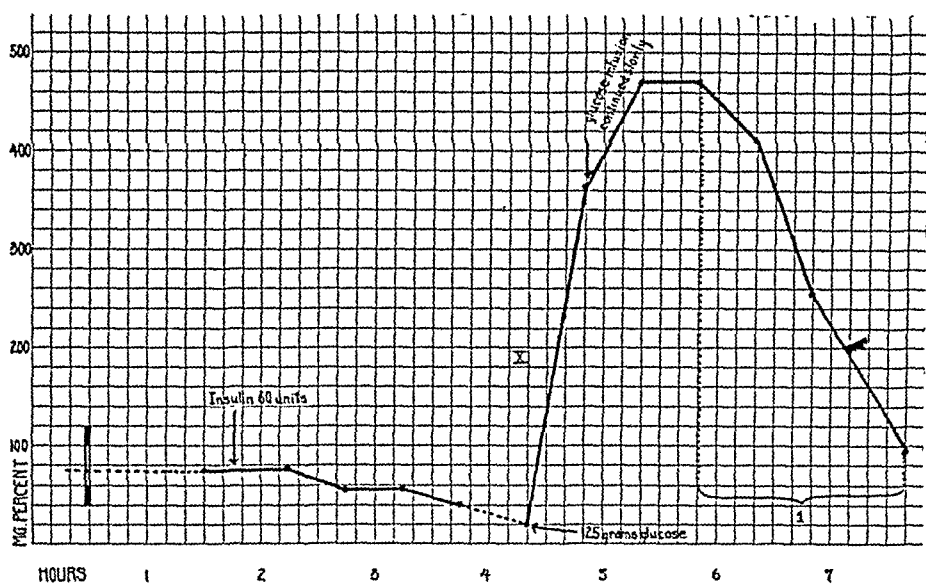


Fig. 10.—Case 10. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	1 hr. 50 min.	204 mg. per hr.	—	—

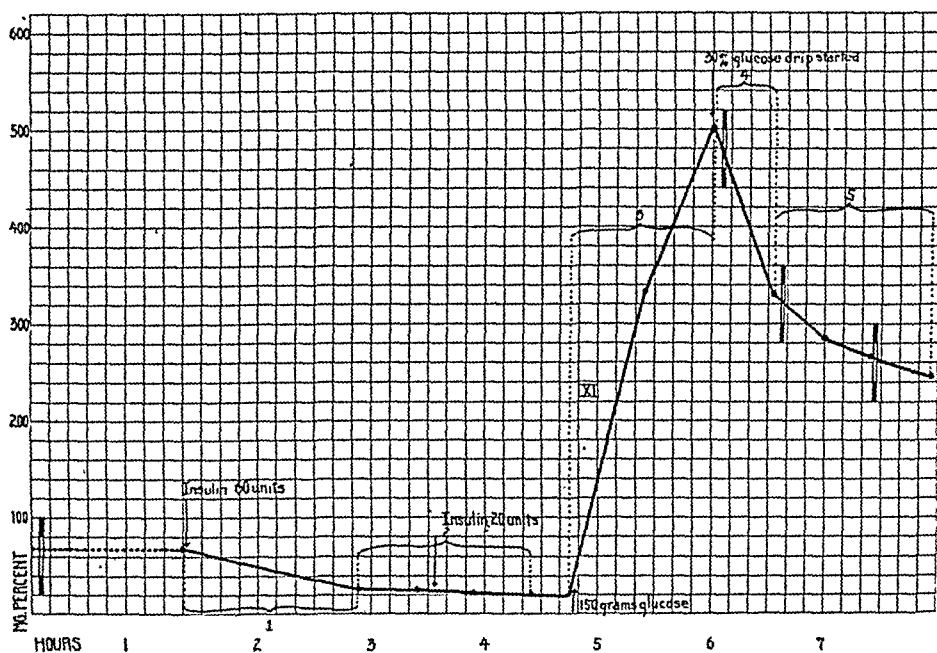


Fig. 11.—Case 11. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	1 hr. 35 min.	26 mg. per hr.	—	—
2	1 hr. 30 min.	6 mg. per hr.	—	—
3	1 hr. 15 min.	Rise of 384 mg. per hr.	—	—
4	32 min.	313 mg. per hr.	1	at 470 mg. %
5	1 hr. 25 min.	64 mg. per hr.	1	at 330 mg. %
			1	at 265 mg. %

tive hypoglycemic levels are sought as has been contended. Cases 6, 11, 13, and 14 showed no increased tendency, to develop convulsions, as the blood sugar was forced from its original level to absolute hypoglycemic levels as compared to the periods during which the blood sugar sought to return to its original level from an absolute hyperglycemia after glucose infusion. Case 8 on the other hand shows a convulsion during a declining period to an absolute hypoglycemia and yet shows no convulsions during a declining period from an absolute hyperglycemia of 580 mg. per cent. When compared with Case 11 we cannot see that this phenomena is of any significance in that the two charts show exactly opposite effects. In the analysis of cases in which the blood sugar was lowered by the use of insulin we find that fifteen convulsions occurred at normal or lower than normal values and seventeen occurred at definitely high values. Convulsions occurred irrespective of the blood sugar concentration ranging from 34 mg. per cent in Case 8 to 705 mg. per cent in Case 12.

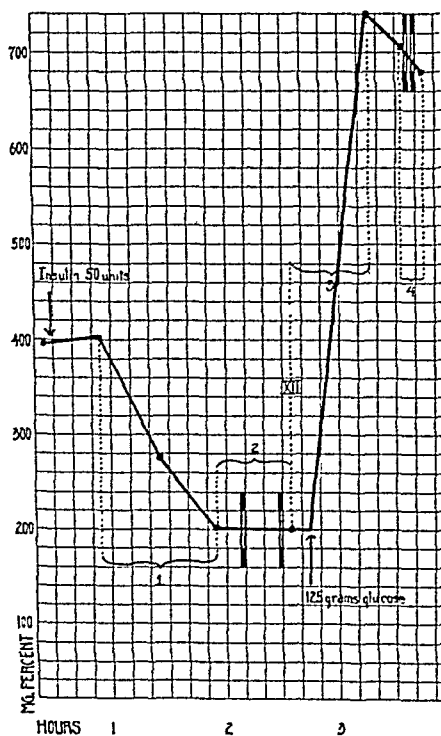


Fig. 12.

Fig. 12.—Case 12. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	1 hr.	200 mg. per hr.	—	—
2	40 min.	9 mg. per hr.	2	at 202 mg. %
3	40 min.	Rise of 810 mg. per hr.	—	—
4	8 min.	188 mg. per hr.	1	at 700 mg. %
			1	at 690

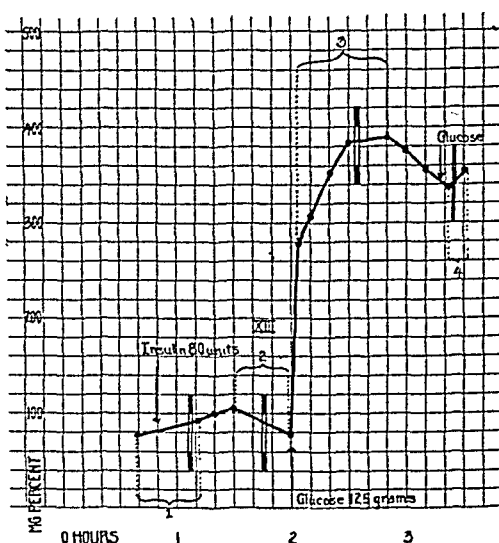


Fig. 13.

Fig. 13.—Case 13. Samples taken at ten-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	31 min.	Rise of 29 mg. per hr.	1	at 93 mg. %
2	30 min.	52 mg. per hr.	1	at 93 mg. %
3	48 min.	Rise of 137 mg. per hr.	1	at 382 mg. %
4	8 min.	Rise of 112 mg. per hr.	1	at 340 mg. %

In view of the fact, as we have previously mentioned, that it is improbable that a convulsion should occur during the rise in blood sugar concentration during the early periods of glucose infusion, we finally present Cases 13 and 14, in which convulsions occur during periods of rapid increase in blood sugar concentration.

The irregular fluctuations in blood sugar in eclampsia, we think, have been indisputably presented. We are inclined, however, to agree with Stander and Harris<sup>5</sup> that many of these minor fluctuations might perhaps be attributed to error inherent in blood sugar determinations. This has been demonstrated by Seigle and Wiley<sup>6</sup> who show errors ranging from 1.1 per cent to over 20 per cent with variations of 0.5 mm. on the scale reading. We also observed during the collection of specimens that the patients were extremely restless and not infrequently had to be restrained. We believe this might at least produce a noticeable variation from time to time. We, therefore, have made an observation of the variations in the blood sugar concentration of

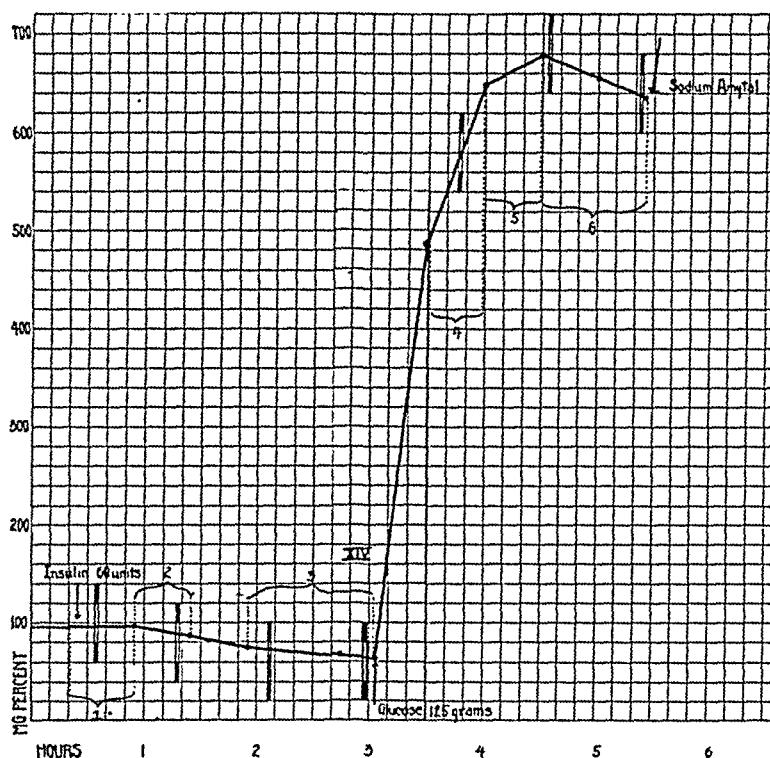


Fig. 14.—Case 14. Samples taken at thirty-minute intervals.

Period	Time	Av. Fall	Convulsions	Sugar Conc.
1	38 min.	0.0 mg. per hr.	1	at 96 mg. %
2	30 min.	24.0 mg. per hr.	1	at 90 mg. %
3	1 hr. 17 min.	15.5 mg. per hr.	1	at 65 mg. %
4	30 min.	Rise of 314 mg. per hr.	1	at 580 mg. %
5	30 min.	Rise of 64 mg. per hr.	1	678 mg. %
6	55 min.	46.0 mg. per hr.	1	(min. later) at 636 mg. %

(Sodium amytal)

a normal primipara which data may be found in Table III. This patient in no way approached the emotional excitability and muscular activity of our eclamptic cases, and yet still showed a variation of 15 mg. per cent over the course of an hour. Although we do not feel that conclusions are justified from this single observation, we suggest that the fluctuations which have been observed in eclampsia may be due to muscular activity and might be observed in a normal patient under the same conditions of excitement and activity.

TABLE III. BLOOD SAMPLES TAKEN AT FIVE-MINUTE INTERVALS. GLUCOSE DETERMINED BY METHOD OF FOLIN ON SOMOGYI FILTRATE.

NORMAL PRIMIPARAS AT MIDDLE OF FIRST STAGE OF LABOR

TIME	BLOOD SUGAR CONCENTRATION
0 min.	84
5	76
10	79
15	74
20	75
25	74
30	74
35	78
40	69
45	75
50	74
55	78

## CONCLUSIONS

1. Neither hypo- nor hyperglycemia is characteristic of eclampsia. The blood sugar concentration probably depends upon the patient's nutritional state and the degree of emotional stability and muscular activity immediately preceding the taking of the specimen.

2. The absolute blood sugar concentration has no effect whatsoever on the incidence of convulsions.

3. Convulsions occur independently of the rate of decline in blood sugar concentrations.

4. Convulsions occur during a rapid rise in blood sugar concentration as well as during a rapid decline.

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Vignes treated a primipara who had hydramnion with calomel suppositories and intramuscular injections of iodized oil for almost twelve weeks until labor set in. By means of a graph he demonstrates the effect this medication had in stabilizing the height of the uterus. Labor was normal and a normal child weighing 3,800 gm. was delivered. The father of the child was found to have leucoplakia and unequal pupils. The placenta on histologic examination demonstrated changes almost certainly indicative of syphilis.

J. P. GREENHILL.

## CONGENITAL ANEMIA OF THE NEWBORN

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**D**URING the past few years a newly described form of anemia affecting newborn infants has attracted attention in the pediatric literature. Since the obstetrician has the first opportunity to observe the disorders of the neonatal period, we hope that his interest in this obscure disease will be stimulated. Early recognition and prompt institution of the proper treatment may be life saving.

Congenital anemia of the newborn may be defined as a hyperchromic anemia of unknown etiology that appears at birth or within the first two weeks of life in full-term and premature infants born of healthy parents. Since 1919, when Ecklin first described a case of unexplained anemia in a newborn infant, approximately fifty cases have been reported in the literature from this country and abroad.

### INCIDENCE

At the Morrisania City Hospital we found three cases in 6,000 births. The clinical diagnosis was made on the appearance of marked pallor. Perhaps, in addition, several mild cases might have been discovered if blood counts had been performed routinely on all newborn infants.

The anemia usually makes its appearance between the third and the tenth day of life. In some cases the anemia has been noted at birth. Both sexes are equally affected. All recorded cases have been in the white race. We report here for the first time a case in a negro infant. The occurrence of congenital anemia of the newborn in several offsprings of the same parents has been noted a number of times including one report in three successive siblings. It has been described in one of twins. With the exception of two cases reported by Akerren, no cases have been recorded in which congenital anemia occurred in the first born. Why the first born is spared is at present unexplained.

The familial association of congenital anemia and of icterus gravis neonatorum has been noted several times. We recently reported a case in which congenital anemia and universal hydrops of the fetus occurred in successive siblings.

### SYMPTOMATOLOGY

Pallor is the only characteristic symptom of congenital anemia of the newborn. This may appear at any time within the first two weeks

of life, and early, may be masked by jaundice. However, when the jaundice clears, the waxy yellow color becomes evident. Icterus is not a constant symptom. It has been noted in about one-half of the reported cases. It appears earlier than the physiologic icterus of the newborn and is usually mild. Vomiting is a frequent symptom. In isolated instances edema of the eyes and of the scrotum has been noted. Petechiae and purpuric spots have occurred in a few cases. Occasionally the liver and spleen have been markedly enlarged. The spleen has been palpable in only about one-half of the reported cases. Hypertrophy of the heart has been noted in a few instances.

Despite the intense anemia the infant does not appear to be very sick. He takes his feedings well and usually gains in weight. There is no fever and no gross bleeding. With recovery all symptoms promptly disappear. The liver, spleen and heart rapidly return to normal size. The pallor persists somewhat longer. Recovery is complete by the third to the sixth month. Some cases which have been followed for several years have shown no late sequelae.

#### DIAGNOSIS

All causes of secondary anemia must be excluded. Among the more frequent of these are congenital syphilis, sepsis, and hemorrhagic disorders. Much more rarely icterus gravis neonatorum, neoplasms, congenital malformations of the cardiovascular system, tuberculosis, diphtheria, and malaria are responsible for anemia in the neonatal period.

#### BLOOD PICTURE

In the normal newborn infant the erythrocyte count ranges from 5,000,000 to 8,000,000; the hemoglobin is correspondingly high (95 per cent to 120 per cent). The blood picture in congenital anemia is of the hyperchromic type. The degree of anemia varies considerably. The most severe case recorded was reported by us (hemoglobin 8 per cent; erythrocytes 400,000). The erythrocytes are large and well filled with hemoglobin, giving a color index of 1 or above. Anisocytosis and poikilocytosis are usually marked. Polychromatophilia, basophilic stippling, normoblasts, megaloblasts, Cabot ring bodies, and reticulocytes may be present early but usually become more marked with the beginning of recovery. When improvement is well established these signs of blood regeneration rapidly disappear.

The leucocyte count is generally within the normal range of 10,000 to 25,000 although a slight degree of leucocytosis may occur. The differential count, platelets, bleeding and coagulation time and the fragility tests are normal. Early in the disease the icteric index is increased.

## PATHOLOGY

Four detailed autopsy protocols including one of our own have been reported. Two cases showed marked erythropoietic activity in the bone marrow and extramedullary foci (Susstrunk, Schleussing). One case showed few erythrocytes or erythroblasts in the bone marrow but considerable erythroblastic activity in the liver and spleen (Happ). In our fatal case there was no evidence of erythroblastosis. The liver and spleen showed a myeloid hyperplasia. Petechial hemorrhages were present in three of the four cases.

## ETIOLOGY

In general, the theories fall into one of two groups: (a) Defective blood formation; (b) Excessive blood destruction.

*Defective Blood Formation.*—1. *Nutritional deficiency:* This theory is based on the assumption that the mother's diet during pregnancy has been inadequate in blood-forming elements. There is no evidence to support this theory. 2. *Toxin production:* A theoretical possibility but also with no evidence in its support is that a toxin arising from either the mother or the fetus depresses the activity of the blood-forming organs. The general good health of the mother and child speak against this theory. 3. *Congenital hematopoietic hypofunction:* The development of the erythropoietic system during fetal life does not keep pace with the other systems of the body so that at birth when the latter are fully developed, the erythropoietic system is still in the fetal stage. A modification of this theory is that at birth or shortly after there is a temporary inhibition of the usual activity of the hematopoietic system. Anemia develops because the normal destruction of mature red cells continues but no new cells are produced to compensate for the loss. 4. *Erythroblastosis:* According to this concept there is a persistence or a reversion to the embryonic level of blood formation due to a primary metabolic disturbance of the hematopoietic system. The result is that immature nucleated red cells are released into the peripheral circulation in large numbers and undergo early destruction.

*Excessive Blood Destruction.*—*Hemolysis* has been suggested as a possible cause of anemia in the newborn. The frequent absence of jaundice is explained by the ability of the liver to excrete the pigment.

## PROGNOSIS AND TREATMENT

There is a striking tendency to spontaneous recovery. The mortality rate in the reported cases is approximately 12 per cent. Many mild cases are probably unrecognized and recover without treatment.



Moderately severe cases, with hemoglobin above 30 per cent, also often show a steady improvement without therapy. If the hemoglobin falls below 30 per cent, immediate transfusion is imperative. Transfusion must be repeated if continued improvement does not follow. A number of cases have required two or three transfusions.

Iron, liver extract and quartz lamp therapy have been used with apparent success, but it is difficult to gauge their therapeutic value because the disease has a decided tendency to spontaneous improvement. There does not seem to be an iron deficiency (Case 3). In this case the infant made a complete recovery without therapy and on breast milk feeding which is poor in iron.

#### CASE REPORTS

CASE 1.—E. P., a white full-term infant, the second child of healthy parents, was born on May 26, 1930, after an easy breech delivery. The birth weight was 7 pounds 5 ounces. Jaundice and pallor were noted on the second day. As the jaundice gradually diminished, the skin assumed a waxy yellow appearance. The spleen was palpable. Blood examination on the fifth day showed: erythrocytes 400,000, hemoglobin 8 per cent, color index 1.0, platelets 242,000, coagulation time five and one-half minutes, bleeding time twenty-two minutes, leucocytes 16,880 with polynuclears 25 per cent, lymphocytes 53 per cent, metamyelocytes 13 per cent, myelocytes 7 per cent, and monocytes 2 per cent. There was an occasional normoblast but no megaloblasts. A transfusion was ordered but the baby had a sudden collapse and died within an hour. At postmortem examination there was found a myeloid hyperplasia of the liver, spleen, and bone marrow with almost complete absence of erythropoiesis.

Two subsequent pregnancies in the same mother resulted in premature stillbirths showing universal edema. Autopsy performed on the second fetus showed, on gross inspection, generalized edema with fluid in the various body cavities. Microscopic sections failed to show evidence of increased erythroblastic activity.

*Comment.*—We have reported these cases in detail elsewhere including illustrations of the histologic sections. We repeat this brief summary here to point out several important features. The association of these two diseases in siblings points to a common etiologic factor and a familial association. There was an absence of abnormal erythroblastic activity in both the cases of congenital anemia of the newborn and of universal edema of the fetus. This case of congenital anemia represents the severest form. Possibly earlier recognition and treatment would have resulted in recovery of the patient.

CASE 2.—P. H., a white full-term male infant, was the fourth child of healthy parents. The first two children are well. The third pregnancy terminated in the birth of a macerated fetus one month prior to term. The prenatal course in the fourth pregnancy was normal. The delivery was spontaneous. The infant weighed 7½ pounds at birth and appeared normal. Jaundice was noticed on the second day; and pallor was noted on the sixth day. The liver was palpable 3 cm. below the costal margin and the spleen was down to the umbilicus. There was no vomiting, edema, bleeding, or fever. The mother's blood count was normal and the Wassermann test was negative.

Blood count on the eighth day showed: erythrocytes 1,200,000, hemoglobin 29 per cent, color index 1.2, and leucocytes 25,000. Differential count showed polynuclears

50 per cent, lymphocytes 43 per cent, monocytes 2 per cent, myelocytes 4 per cent, myeloblasts 1 per cent. There were 16 normoblasts per 100 white cells counted. The smear showed moderate anisocytosis, poikilocytosis and polychromatophilia.

Transfusion of 30 c.c. of blood was given with considerable but only temporary improvement. Another transfusion of 40 c.c. was given one week later. Improvement was now sustained and no further treatment was required. Following the second transfusion, the child developed an upper respiratory infection complicated by a bilateral otitis media which cleared up promptly. At the age of five months there was a recurrence of the middle ear infection. At six months, the red blood cell count was 5,570,000 and the hemoglobin 105 per cent. The weight curve has

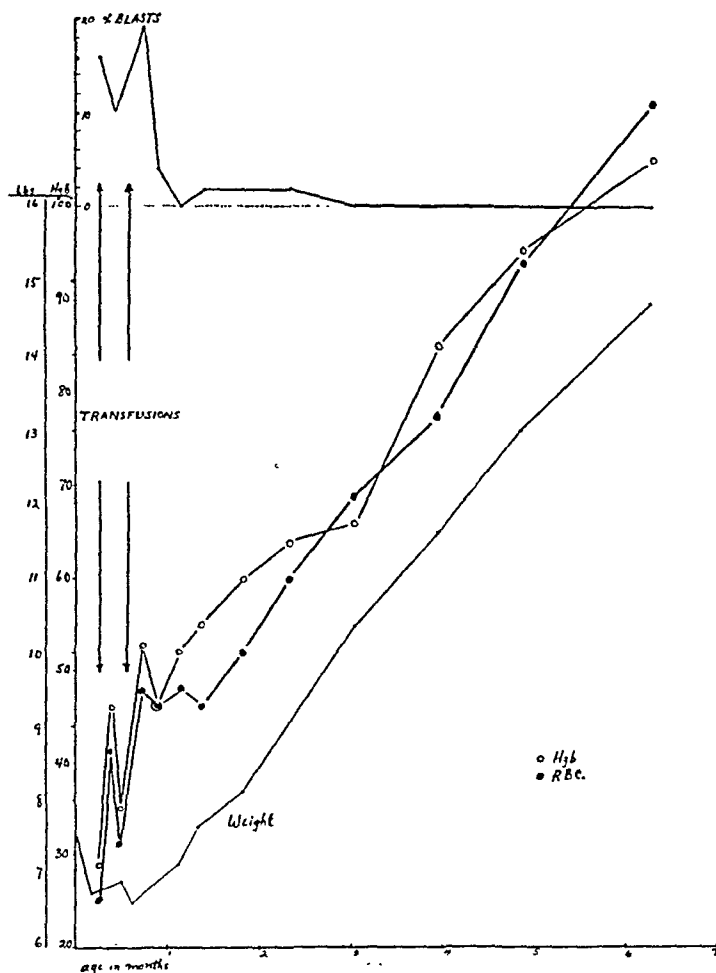


Fig. 1.—Case 2.

also paralleled the erythrocyte and hemoglobin curves. The normoblasts rapidly disappeared from the peripheral blood.

*Comment.*—This case is a typical severe form of congenital anemia of the newborn. The presence of 16 normoblasts per hundred white cells indicates an active attempt at regeneration. It required two transfusions to give the proper impetus to normal erythropoiesis.

CASE 3.—O. B., a full-term male infant, was the third child of healthy negro parents. The first two children are alive and well. The third pregnancy was uneventful and terminated on Oct. 1, 1933, in the spontaneous delivery of an infant weighing 6½ pounds who appeared normal at birth. The mother's blood count was normal and the blood Wassermann test on both parents was negative. On the

eight day it was noted that the infant was pale. The liver and spleen were not palpable but the heart was slightly enlarged.

Blood count on the ninth day showed: erythrocytes 1,480,000, hemoglobin 38 per cent, color index 1.3, leucocytes 14,150. Differential count showed: polynuclears 52 per cent, lymphocytes 46 per cent, monocytes 1 per cent, and myelocytes 1 per cent. There was one normoblast per one hundred white cells counted. The smear showed slight anisocytosis, poikilocytosis and polychromatophilia. Repeated examination of wet blood smears failed to show any sickling of the red cells.

The infant was breast fed and kept under observation at home without any treatment. At twenty days, the red blood cell count had risen to 2,270,000 and the

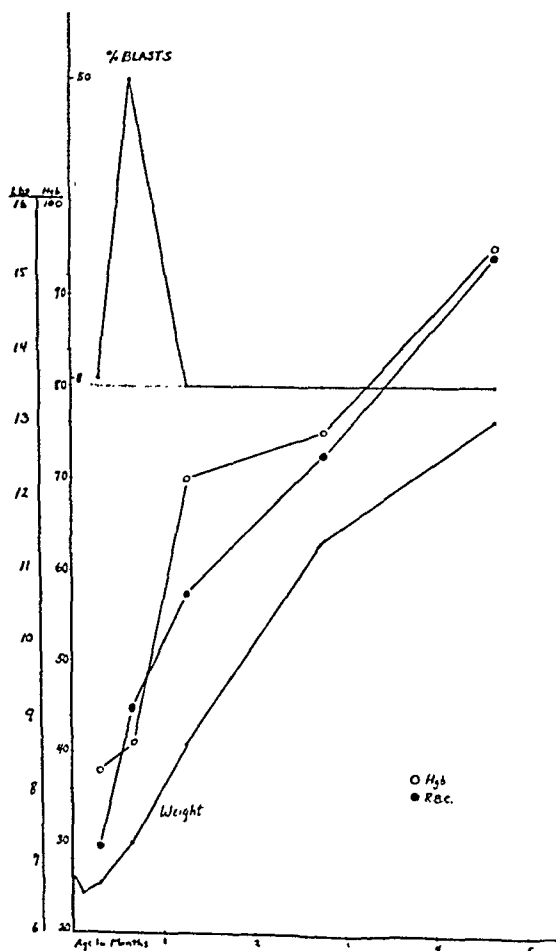


Fig. 2.—Case 3.

hemoglobin was 41 per cent. The striking feature, however, was the very marked evidence of regenerative activity present in the blood smear at this time. There were 50 nucleated red cells per one hundred white cells of which 90 per cent were normoblasts and the remainder megaloblasts. In addition, marked polychromatophilia, basophilic stippling and numerous Cabot ring bodies were present.

Seventeen days later, the hemoglobin had risen to 70 per cent and the erythrocytes to 2,870,000. No nucleated red blood cells were seen. The weight curve also continued to rise. At four and one-half months, the blood count showed a hemoglobin of 95 per cent and erythrocyte count of 4,750,000.

*Comment.*—This is the first recorded instance in which congenital anemia of the newborn occurred in a negro infant. No evidence of sickle-cell anemia was present. The occurrence of 50 nucleated red cells per 100 white cells at twenty days of age

as compared with one at eight days of age would seem to indicate that erythroblastemia is a secondary response rather than the basic pathologic disorder. Furthermore this case illustrates that recovery may occur without any therapy and despite an iron poor diet.

CASE 4.—L. K., a normally appearing full-term infant, was delivered by median forceps on Feb. 21, 1934. She was the second child, the first being a stillborn following a placenta previa. Her birth weight was 8 pounds 13 ounces. Soon after birth it was noticed that she was pale but no particular significance was attached to this observation. She took her feedings well but did not gain. We saw this baby for the first time at the age of twenty days. Her weight was 8 pounds 5 ounces.

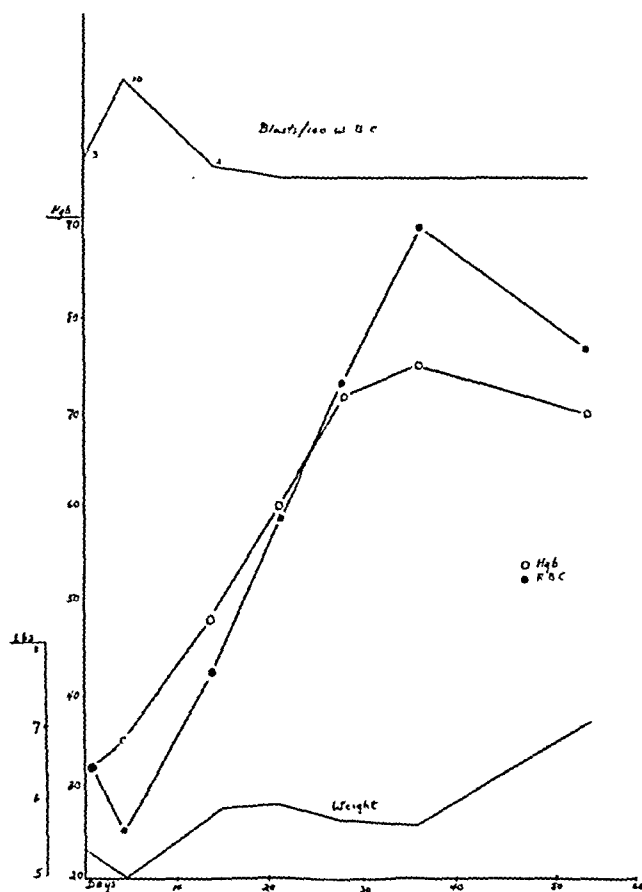


Fig. 3.—Case 5.

She appeared definitely pale. There was no history of jaundice. The physical examination revealed no abnormalities except a healing fracture of the clavicle. The liver and spleen were not enlarged. Blood examination on the same day showed: erythrocytes 2,950,000, hemoglobin 72 per cent (Sahli), color index 1.2, reticulocytes 6 per cent, no nucleated red blood cells, moderate anisocytosis and poikilocytosis, slight polychromatophilia, leucocytes 11,350, lymphocytes 57 per cent, polynuclears 39 per cent, eosinophiles 2 per cent, and monocytes 2 per cent. Platelets were abundant on smear. The bleeding time was three minutes and the coagulation time four minutes.

*Comment.*—This case, which has just come under our observation, is cited to illustrate the mild type of congenital anemia of the newborn, usually overlooked, and one that recovers spontaneously. Its practical importance is that the infants of future pregnancies in this mother require close watching. Early discovery of a

severe anemia or icterus gravis neonatorum in a subsequent pregnancy with prompt transfusion may become a life-saving measure.

CASE 5.—F. McC., a white male infant weighing 3 pounds 15 ounces, was born on Aug. 24, 1930, three weeks prior to term. The mother had one previous pregnancy in 1929 which resulted in a miscarriage. Both parents were in good health. About a month before the expected termination of the present pregnancy, the mother developed a mild toxemia and labor was induced a few days later. Delivery was spontaneous and the puerperium uneventful. The Wassermann test of the blood of the mother and the infant was negative.

The infant appeared to be fairly sturdy at birth; it took its feedings well and gained in weight. There was no jaundice. During the second week, however, pallor

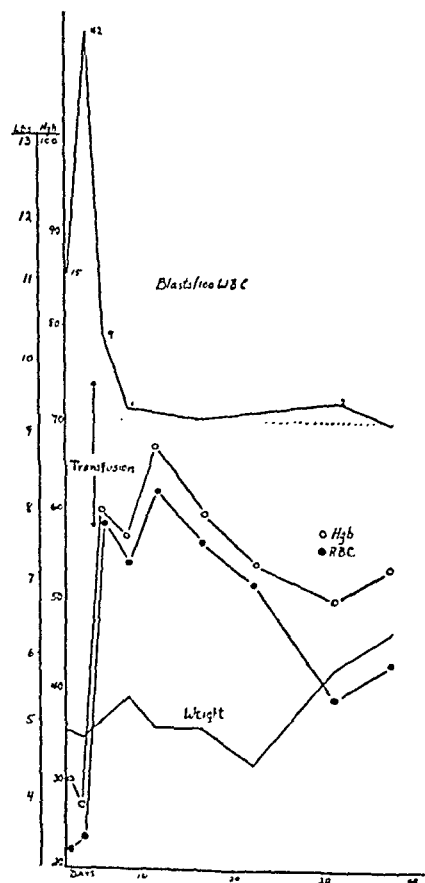


Fig. 4.—Case 6.

gradually developed. The infant was sent home when it was three weeks old and weighed five pounds. One week later, it was readmitted to the hospital because of vomiting and dehydration (pylorospasm). Pallor was now very pronounced. The spleen was palpable 3 cm. below the costal margin but the liver was not enlarged. The vomiting was soon controlled with atropine although a mild fever was present during the administration.

The first blood count, performed when the infant was one month old, showed: erythrocytes 1,600,000, hemoglobin 32 per cent (Sahli), color index 1.0, leucocytes 15,000, lymphocytes 62 per cent, polynuclears 30 per cent, monocytes 4 per cent, and myelocytes 4 per cent. The platelet count was 250,000; the bleeding time, four minutes; and the coagulation time, four minutes. The smear showed 2 normoblasts per 100 white cells counted and moderate polychromatophilia, anisocytosis, and poikilocytosis.

The infant was given short daily exposures of ultraviolet ray and 15 c.c. of whole blood intramuscularly for ten days. Preceding the rapid rise in the erythrocyte count and hemoglobin, there was a transient increase of the normoblasts to 10 per hundred white cells. The spleen soon decreased in size. When the infant was three months old, the erythrocyte count had risen to 3,850,000 and the hemoglobin to 70 per cent.

*Comment.*—A blood count was not made until the infant was one month old although pallor was noted during the second week of life. The toxemia of pregnancy in this mother was probably coincidental. Although congenital anemia usually occurs in full-term infants, several instances in premature infants have been reported. Congenital anemia in premature infants should not be confused with the anemia of prematurity which does not appear until after the third month.

CASE 6.—E. K., a white female infant weighing 4 pounds 7 ounces, was born on March 8, 1934, six weeks prior to term. Both parents were in good health. The mother had one previous pregnancy in 1932, which resulted in a miscarriage at the fourth month. When the infant was three days old, it became moderately jaundiced. On the seventh day, it appeared to be very pale. The baby was admitted to the hospital one week later. At this time, the skin was a waxy-yellow color and the liver and spleen were palpable just below the costal margin. The weight was 5 pounds. Blood count on April 4, 1934 showed: erythrocytes 1,100,000, hemoglobin 30 per cent (Sahli), color index 1.3; leucocytes 31,600, polynuclears 27 per cent, lymphocytes 68 per cent, myelocytes 4 per cent, and monocytes 1 per cent. There were 15 normoblasts per hundred white cells counted. The smear showed marked polychromatophilia, poikilocytosis, and anisocytosis, and a few Cabot ring bodies. Blood Wassermann test of both parents and the infant was negative. Blood count of the mother was normal. Two days later, the nucleated erythrocytes had increased to 44 per hundred white cells. The infant was given a transfusion of 55 c.c. of citrated blood through the anterior fontanel on the following day. This was followed by a rise of the erythrocytes to 2,950,000 and of the hemoglobin to 60 per cent. A few days later the jaundice disappeared, the liver and spleen were no longer palpable, and the general appearance of the infant was greatly improved.

*Comment.*—This is another instance of congenital anemia of the newborn in a premature infant. Here again the increase in erythroblasts in the blood two days following the first blood count is striking, and probably signifies an attempt at spontaneous recovery. Because of the severity of the anemia, however, it was deemed safer to transfuse this infant without delay.

#### SUMMARY AND CONCLUSIONS

An increasing number of instances of congenital anemia of the newborn appearing in the pediatric literature seems to indicate that the disease is more common than was at first believed. We desire to bring this disease to the attention of the obstetrician. Early recognition and prompt institution of appropriate therapy will result in the saving of lives.

Congenital anemia of the newborn is described from the clinical, pathologic, and hematologic viewpoints. The familial tendency is noted, as is also the association with icterus gravis neonatorum and with universal edema of the fetus.

The etiology is unknown. It seems to us that the most attractive theory is that of inhibition of the development of the erythropoietic

system. Erythroblastemia appears to be a secondary response to the anemia rather than the underlying pathology.

Five previously unreported cases are described including the first recorded instance in a negro infant.

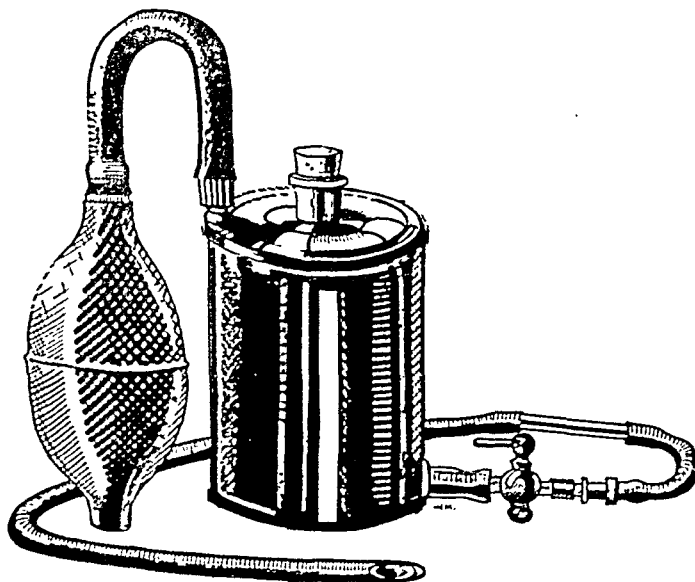
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#### A SIMPLE ETHER OIL APPARATUS

R. P. LITTLE, M.D., SANTA PAULA, CALIF.

**A**N EFFICIENT apparatus for the administration of ether oil per rectum can easily and cheaply be assembled using a Mallinckrodt



ether can as a reservoir and a Becton, Dickinson & Co., stopcock and adapters. A tinsmith can do the soldering necessary in a few minutes.

## TRACTION IN FORCEPS DELIVERIES

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ONE finds discussed in the obstetric literature practically every phase of the use of forceps. The present study was conceived with the idea of determining just how much force must be applied to the forceps in the average case, in order to complete a delivery, and also what effect, if any, certain factors such as parity, color, age, etc., would have on the findings. The data were collected from cases on the Obstetrical Service at Cleveland City Hospital during the year beginning July 1, 1932.

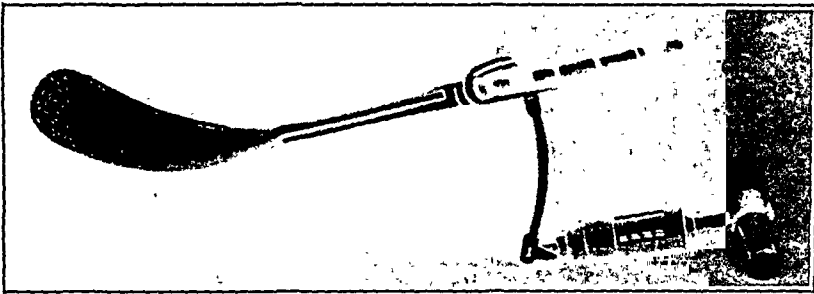


Fig. 1.—The Bill axis traction handle with traction recording modification (tractionometer) in place on Tucker-McLane blades. Traction applied in the direction of the pointer is measured and recorded by a ring which slides over a scale on the side of the mechanism.

The instrument used was a Bill axis traction handle in which a spring mechanism had been inserted, and Tucker-McLane forceps. This set-up insured an accurate application of force in the axis of the birth canal and minimized the resistance offered to delivery by the forceps themselves. The forceps were applied and observations obtained when the head had reached the pelvic floor, or in other cases where the head was engaged, and full dilatation of the cervix had taken place, but where there was undue delay in advancement. Obviously this routine offered an excellent opportunity for a study of this nature since the majority of patients presented no dystocia and, therefore, the findings represent for the most part the normal resistance encountered by the presenting part in the completion of the second stage of labor.

To further facilitate delivery the procedure of "ironing-out" the birth canal was used, employing a lubricating soap freely during this process. With the vagina and perineum well dilated and lubricated,



an accurate cephalic application of the forceps was then made. Traction, however, was not exerted until, by abdominal palpation, a uterine contraction was detected. The blades were then locked, the claw of the handle slipped into place and traction applied. This force was exerted only for the duration of the uterine contraction and an effort was made never to exceed the least amount of traction needed to advance the head. At the end of the contraction the head was allowed to slip back into the hollow of the sacrum, the handle removed, and the blades opened. At this time the maximum traction exerted during the preceding pull was read from the scale, and the recording ring of the instrument returned to zero. This procedure was then repeated during as many contractions as were necessary, until the head came down under the symphysis far enough to be grasped through a "chin towel." The blades were then removed and the completion of the delivery over the perineum done by hand.

During the period of this study 1,521 patients were delivered. In 1,068 (69.5 per cent) of these, forceps were used. Traction observations were made on 880 cases from this group. These were unselected with the exception of 13 cases that required the use of Tarnier blades, and hence could not be included in this series.

The data collected, as already stated, consisted of a series of figures representing the maximum traction, in kilograms, recorded in each pull of a series of pulls necessary to complete the second stage. There was the most extreme variation encountered between individual cases, not only in amount, but also in the number of pulls required. For example, among the primiparas the range was from a single pull of 5 kilograms to a series such as: 15-14-18-19-21-23-21-21-13-12 or in another case 26-27-27-30-29-28-23-12. Among the multiparas there were 64 patients delivered by single pulls of less than 5 kg., but here too the higher figures were sometimes reached, as in a case delivered by pulls of 20-24-25-25-27-27-33. The maximum traction recorded in any single pull was 34 kg. (74.8 pounds). The maximum number of pulls in any single case was 10.

It is obvious then, that, with such extreme variations from case to case, deductions to be of any value must be based on averages from a fairly large series of cases. With this in mind we have calculated our results in the various groups on the basis of, first, the average individual pull, and second, the average number of pulls. The force of the individual pull is, of course, the important factor so far as trauma to the mother or baby is concerned but, in order to get a true picture of the difficulty encountered in any particular case or class of cases, the number of such pulls needed to complete the delivery is also important. So, in calculating our results we have taken the product of the average individual pull times the average number of pulls in any series of cases, as the index of resistance encountered in that group.

This "Resistance Index" we believe, gives a fair estimate of the relative difficulty encountered on various groups of patients.

Employing the methods just discussed, the cases were studied according to various factors which it was thought might have a bearing on the ease or difficulty of delivery.

#### PARITY

The number of babies previously borne by a mother should be an important factor. Study of our data gave results as shown in Table I.

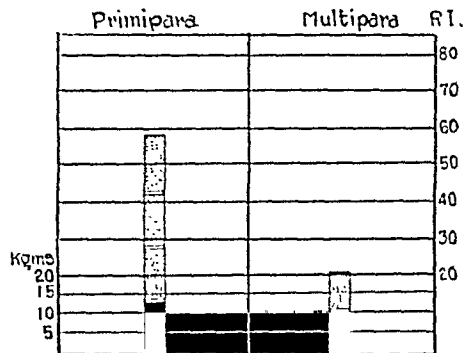


Fig. 2.—Graph showing the relative resistance found in primiparas and multiparas. Data from Table I. Key: Blocks represent the average individual pull, in kilograms. The number of blocks corresponds with the average number of pulls for the group. The resulting column represents the resistance index of the group.

It is immediately obvious that the greatest difference lies between the primipara and the multipara. In the latter group the para ii's are definitely higher than any of the others; above para v there appears to be a tendency to increasing resistance with higher parity.

On direct comparison of the multipara and primipara averages, we find that the resistance index has a relationship of 1 to 2.7. On the other hand, when the average individual pull is compared the relationship is only 1 to 1.4. This difference is compensated for by the increased number of pulls used in the primiparous cases. As has already been mentioned, it is reasonable to assume that injury, if any, will be the result of the more forceful pulls; it would seem logical, therefore, to keep the

TABLE I. PARITY

GROUP	CASES	AVERAGE PULL	AV. NO. PULLS	RESISTANCE INDEX
Primiparas	321	15.45 Kg. (34.0 pounds)	3.7	57.2
Multiparas	559	11.15 Kg. (24.5 pounds)	1.9	21.2
Para ii	244	11.97 Kg. (26.3 pounds)	2.1	25.1
iii	122	9.87 Kg. (21.7 pounds)	1.6	15.8
iv	76	9.68 Kg. (21.3 pounds)	1.7	16.5
v	34	10.25 Kg. (22.6 pounds)	1.5	15.4
vi	32	10.45 Kg. (23.0 pounds)	1.7	17.8
Over vi	51	11.15 Kg. (24.5 pounds)	1.8	20.1

maximum pull as low as possible and encourage a distribution of the energy over an increasing number of pulls as the delivery becomes more difficult. This policy was carried out as far as possible in the present study. It would be purely speculative but interesting to imagine what the results would have been, both as to force exerted and also on our morbidity and mortality data, had each delivery been com-

pleted by a single adequately forceful pull. Certainly, since the resistance encountered would have remained the same in each instance, the maximum effort exerted would have reached much higher levels which one would expect to see reflected in the end-results.

Another factor that should be repeated and emphasized is that traction was only applied during a period of uterine contraction, and was seldom sustained for more than about thirty seconds. In this way the damage was minimized which might be expected to follow prolonged compression of the fetal head and maternal soft parts. This policy also utilizes the expulsive force contributed by the contracting uterus. This is of unknown, and probably quite variable amount, but we feel assured that it was of real value in reducing the traction necessary in the average case.

Since such characteristic differences exist between primipara and multipara averages, we have calculated all our data under these two subdivisions.

*Color.*—Observations as to color offer variations that are of at least academic interest and lend some support to the popular impression that colored women have easier deliveries than white.

TABLE II. COLOR

	CASES	AVERAGE PULL	NO. PULLS	R. I.
Primiparas, white	236	15.95 Kg. (35.0 pounds)	3.9	62.2
Primiparas, colored	85	15.03 Kg. (33.1 pounds)	3.3	49.7
Multiparas, white	441	11.33 Kg. (24.9 pounds)	1.9	21.5
Multiparas, colored	118	10.37 Kg. (22.8 pounds)	1.7	17.6

*Age.*—The study according to age was not very satisfactory among the primiparas, since our cases for the most part fell in the groups between sixteen and thirty years. There were only 17 scattered cases outside this range, obviously not enough to consider. Within this limited range, however, there did appear to be a definite relation between age and traction, and it is possible that in a larger series this trend would have been seen to continue in the higher age groups.

TABLE III. AGE

PRIMIPARAS	CASES	AVERAGE PULL	NO. PULLS	RESISTANCE INDEX
16-20	176	14.84 Kg. (32.6 pounds)	3.5	51.9
21-25	96	15.96 Kg. (35.1 pounds)	3.9	62.2
26-30	32	16.7 Kg. (36.7 pounds)	4.6	71.8

Among the multiparas no significant age variation was discovered.

*Position.*—Observations according to position of the presenting part confirmed to a degree the expected influence of anterior and posterior presentation. The cases

TABLE IV. POSITION

	CASES	AVERAGE PULL	NO. PULLS	RESISTANCE INDEX
Primiparas Ant.	240	14.8 Kg. (32.6 pounds)	3.6	53.3
Primiparas Trans.	23	15.35 Kg. (33.8 pounds)	3.5	53.7
Primiparas Post.	55	17.9 Kg. (39.4 pounds)	4.3	77.0
Multiparas Ant.	484	11.06 Kg. (24.3 pounds)	1.8	19.9
Multiparas Trans.	18	9.69 Kg. (21.3 pounds)	1.4	13.6
Multiparas Post.	55	11.47 Kg. (25.2 pounds)	1.9	21.7

which had engaged and remained posteriors required slightly more effort to deliver, even though they had all been converted into anteriors by means of the Modified Scanzoni maneuver, before any traction was applied. These differences can reasonably be attributed to lack of molding. However, the differences are surprisingly small and would tend to indicate that while molding is of unquestioned importance in some cases, it is not of great significance in the average posterior case. We find a moderate increase of traction in the primiparas, posterior class, but among the multiparas this difference is negligible.

The figures for the transverse presentation are unexpectedly low, but since they are based on such a small group of cases we prefer to attach no particular importance or interpretation to them.

*Type of Forceps Application.*—When the cases are studied on the basis of type of forceps application, a more definite and important trend is demonstrated. Our series did not include any high applications and only ten high-midforceps, certainly not

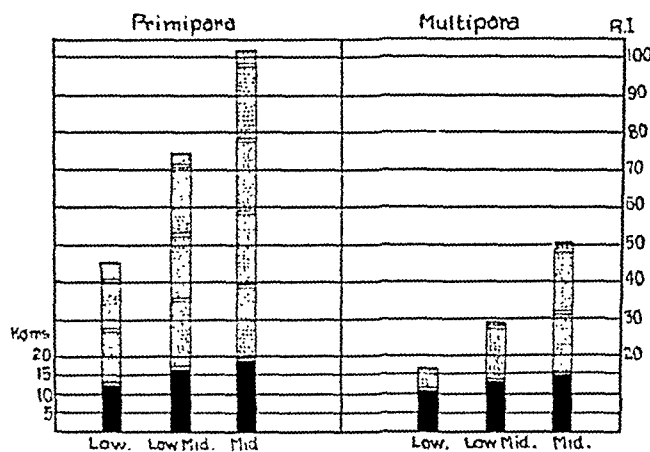


Fig. 3.—Graph showing relative resistance encountered, depending upon the type of forceps application. Data from Table V. (Key as in Fig. 2.)

enough to be significant. In the low, low-mid, and mid groups, however, the results were more definite and illustrate clearly the increasing difficulty one may expect to encounter when the head fails to descend after a moderate trial of second stage labor.

TABLE V. TYPE OF FORCEPS APPLICATION

	CASES	AVERAGE PULL	NO. PULLS	RE-SISTANCE INDEX
Primiparas, low	192	13.7 Kg. (30.1 pounds)	3.3	45.2
Primiparas, low-mid.	106	17.4 Kg. (38.3 pounds)	4.3	74.8
Primiparas, mid	15	19.31 Kg. (42.5 pounds)	5.3	102.3
Multiparas, low	434	10.03 Kg. (22.1 pounds)	1.7	17.1
Multiparas, low-mid.	101	13.3 Kg. (29.3 pounds)	2.2	29.3
Multiparas, mid	16	15.77 Kg. (34.7 pounds)	3.2	50.5

*Trauma to Birth Canal.*—Further study of the data demonstrated an interesting association between trauma and traction whereby the degree of trauma and the force exerted increased together. This is observed in both the primipara and multipara groups. The most logical explanation would seem to be that both trauma and increased resistance are brought about by either a relatively larger baby or by less elastic maternal tissues, or both.

Episiotomy in our series was performed only when a severe second-degree or third-degree laceration seemed inevitable. This group, therefore, properly follows the second-degree group in degree of trauma. There were no third-degree tears.

The data presented relative to cervical tears is interesting but somewhat distorted, not only due to the small number of cases but also due to the fact that the cervix was only inspected following a difficult labor or delivery that suggested probable damage at this site.

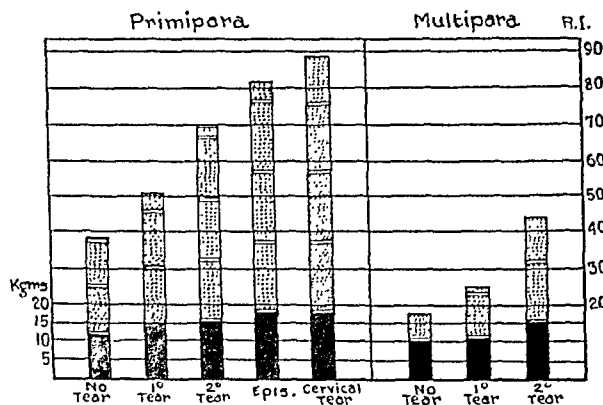


Fig. 4.—Graph showing the relative resistance encountered in groups arranged according to the degree of trauma to the birth canal. Data from Table VI. (Key as in Fig. 2.)

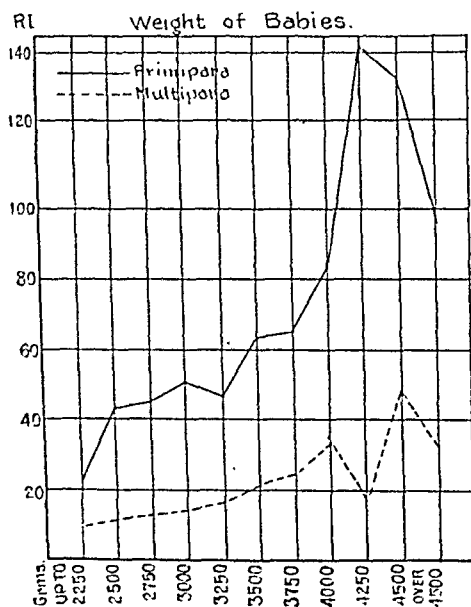


Fig. 5.—Graphs showing the relative resistance encountered in groups arranged according to the weight of the babies. Points plotted represent the resistance index for each weight group.

*Weight of Babies.*—The size of the baby is, of course, an important factor in determining the ease or difficulty of delivery. In Fig. 5 the weight of the babies has been plotted against the resistance index in the various size groups. Unfortunately, there were too few cases in some of the groups to give a true average, with a corresponding smooth curve, but the trend is quite obviously that of increasing resistance with increasing size of the baby. This is true in both the primiparous and multiparous groups.

TABLE VI. TRAUMA

	CASES	AVERAGE PULL	NO. PULLS	RE-SISTANCE INDEX
Primiparas, no tears	81	12.25 Kg. (27.0 pounds)	3.1	38.0
Primiparas, 1° tears	95	14.48 Kg. (31.9 pounds)	3.5	50.7
Primiparas, 2° tears	102	17.0 Kg. (37.4 pounds)	4.1	69.7
Primiparas, episiotomy	28	18.02 Kg. (39.6 pounds)	4.6	82.9
Primiparas, cervical T.	16	18.7 Kg. (41.1 pounds)	4.7	87.9
Multiparas, no tears	452	10.06 Kg. (22.1 pounds)	1.8	18.1
Multiparas, 1° tears	78	12.16 Kg. (26.8 pounds)	2.1	25.5
Multiparas, 2° tears	26	15.38 Kg. (33.8 pounds)	2.8	43.1

From the data so far presented an interesting correlation was observed between the size of the baby and certain other factors. From the data on primiparas we get the figures shown in Table VII.

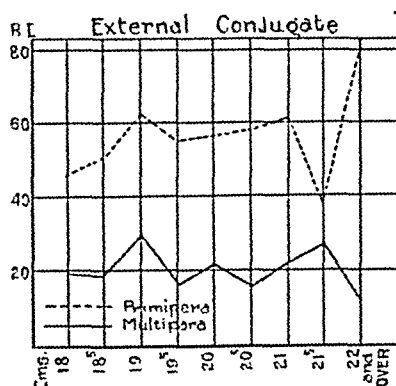


Fig. 6.

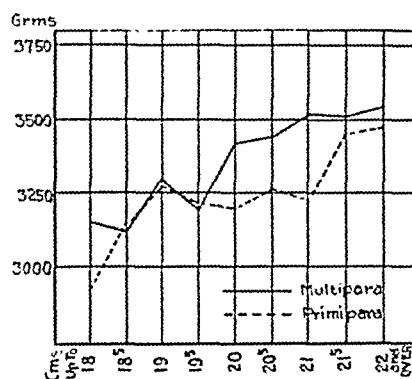


Fig. 7.

Fig. 6.—Graph showing the relative resistance encountered in groups arranged according to the measurement of the external conjugate. Points plotted represent the resistance index for each size group.

Fig. 7.—Graph showing the average weight of babies in groups arranged according to the measurement of the external conjugate.

While there are many interacting factors which make the problem too complex for complete analysis, we feel that probably in the majority of cases a relatively large baby is the primary cause of not only the higher forceps application, but also of the increased resistance and trauma as well, rather than that any of these factors bear a direct cause and effect relationship to each other.

TABLE VII

	RESISTANCE INDEX	TEARS OF ALL DEGREES	AVERAGE WT. OF BABIES
Low forceps	45.2	65.6%	3,133 gm.
Low-midforceps	74.8	84.0%	3,264 gm.
Midforceps	102.3	100.0%	3,304 gm.

*Size of Pelvis (External Conjugate).*—The size of the pelvis, as expressed by the external conjugate would also seem to be a good index of the probable resistance to be encountered at delivery. This impression, however, is not borne out. Among the multiparas the traction needed for delivery remained practically the same regardless of this measurement, while among the primiparas, there was an actual tendency for deliveries to become more difficult as the external conjugate became larger.

The answer to this is obvious when the weight of babies is plotted against the size of the pelvis (Fig. 7), it then becomes apparent that any advantage gained by the larger pelvic measurement is lost due to increased size of babies in these cases.

*Morbidity and Mortality.*—There were 14 mothers (1.6 per cent) who developed serious complications such as phlebitis, metritis, etc., following delivery. These might be attributed to trauma; however, the actual traction was found to be well below the average in these cases. Two mothers were lost, both from septicemia (2.2 per 1,000). One, a primipara, was delivered by traction moderately in excess of the average. The other, a multipara was delivered by traction far below the average.

Considering the infant mortality, there were 31 stillbirths and neonatal deaths, giving a gross mortality of 3.4 per cent. The causes of death were diagnosed as follows: Prematurity, 9; macerated stillbirth, 2; pneumonia, 5; hemorrhagic disease of N. B., 1; premature separation of placenta, 2; infection, 1; congenital deformity, 2; asphyxia neonatorum, 9. Autopsies were performed on 26 or 84 per cent of these. In none was cerebral hemorrhage found. Two of the babies diagnosed as asphyxia neonatorum were not posted, however; they had presented no clinical evidence suggestive of cerebral injury and the traction exerted had been far below the average in each case. Three of the asphyxia neonatorum cases had been subjected to traction slightly above the average. In the remaining six, traction was far below the average.

Thus we feel justified in not considering trauma as an important factor in our morbidity and mortality record.

### CONCLUSIONS

The data just presented have been prepared with the idea of making certain academic observations on the amount of force involved in routine forceps work. For this reason the exact methods employed have been described in some detail, since comparisons and interpretations can only be made with these details in mind. It should also be pointed out that in routine work it is very difficult to set up any satisfactory division in the records between "prophylactic" or elective forceps and truly operative causes. For this reason the averages presented here include many cases which would have been operative cases in the hands of the most conservative. In addition, some of the persistent occiput posteriors handled in this series by the Modified Scanlon maneuver and forceps extraction, would in other clinics be delivered in some other way. It is, therefore, obvious that our averages are somewhat above those which one would obtain from truly normal "elective forceps" cases, but they do represent routine forceps findings.

The question of what relationship exists between these traction figures and the force which the patient herself would have to exert delivering the same baby spontaneously, is one which does not permit of any but a speculative answer. The traction figures represent an equivalent amount of resistance to delivery. This resistance would remain practically the same to spontaneous delivery; thus the amount of spontaneous effort required would at least be proportional, if not equal, to that actually recorded.

Our own opinion is that if it were possible to measure spontaneous effort, there would be found a fairly close correspondence between the force exerted in a spontaneous expulsion and the figures presented here, with the exception that the forceps extraction, being mechanically more efficient, would reduce the effort required to a moderate extent in this form of delivery. In the posterior cases, however, we believe the effort required to complete delivery following a Modified Scanzoni is only a fraction of that which the mother would have to exert in order to rotate the head and deliver the same baby herself.

As for the use of the tractionometer, we found it of great value as an aid in teaching new men. It was observed that men with considerable experience had no idea how hard they pulled in terms of pounds or kilograms. It was, therefore, impossible to tell a beginner how hard to pull or to know how hard he was pulling during a delivery. Using this appliance, however, it is possible to suggest the probable traction required and at all times to know just how much force is being exerted and to alter this as occasion arises. To the experienced operator himself, traction readings act as a definite incentive for increased gentleness and accuracy in forceps work.

Finally, the inclusion of these readings in the case history gives a direct record of just how difficult the delivery was, and will be a very valuable addition to the hospital files in the event of any follow-up studies on these mothers or babies at some later date.

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Fleurent, Keller, and Meyer: Chorionepithelioma of the Tube, Bull. Soc. d'obst. et de gynéc. 5: 452, 1933.

There are 32 cases of chorionepithelioma of the fallopian tube reported in the literature. Compared with the frequency of extrauterine gestation, chorionepithelioma of the tube is not less frequent than the same affliction of the uterus after uterine pregnancies. In most of the 32 cases reported, the women had had from one to five pregnancies while a few had never before been pregnant.

The diagnosis of chorionepithelioma of the tube presented serious difficulties but the diagnosis was suggested by the following clinical facts: A history of extrauterine pregnancy; an intervening period of a few weeks or months; reappearance of bleeding accompanied by abdominal pain; an adnexal tumor which was growing rapidly; metastases on the vulva or in the vagina; an empty uterine cavity; cachexia and pronounced anemia and the formation of metastases in the body.

The prognosis was grave. Among the 32 cases there were only three recoveries. Treatment consisted not only of removal of the tube containing the tumor and the visible metastases but also of a complete hysterectomy. This was to be followed by roentgen ray applications.

J. P. GREENHILL.



# EXPERIMENTAL STUDIES OF PUERPERAL INFECTION

## V. THE VARIATION IN THE SUSCEPTIBILITY OF THE SKIN TO STREPTOCOCCUS TOXIN DURING PREGNANCY

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AN EXPERIMENTAL study of puerperal infection was undertaken to determine whether susceptibility to the invasion of microorganisms was altered at the time of pregnancy. Our early studies indicated that pregnant mice were more susceptible to infection with hemolytic streptococci inoculated intraperitoneally than were non-pregnant mice. Subsequent studies<sup>1, 2</sup> on the survival of pathogenic bacteria in the vagina, on hemolytic complement, and on the production of agglutinating activity in the serum have failed to reveal any significant immunologic difference between pregnant and virgin rabbits.

Two authors have reported an unusual response to intradermal injections of streptococcus toxin during pregnancy. Weiss<sup>3</sup> tested the reactivity of the skin to this toxin at frequent intervals in a group of pregnant women. Eleven of the patients whose skin reacted to the toxin early in pregnancy failed to show this reaction following delivery. On the other hand, nine patients in whom the tests had been negative originally reacted later on. In another twenty-seven patients, the reaction, while not completely reversing itself, varied in its intensity, becoming either weaker or stronger. Burton and Balmain<sup>4</sup> tested 221 pregnant women and separated 36 with positive reactions from the main group for retesting, which was done at monthly intervals. Sixteen of the women had negative reactions before delivery, but in three patients the reaction reverted to positive at a later date.

Observations made in this laboratory, where goats and rabbits are used in the standardization of toxin, indicate that the skin of these animals also may become insensitive to toxin when they are pregnant. They were, therefore, considered to be suitable for use in a more detailed investigation of this problem.

### METHOD OF INVESTIGATION

Chinchilla rabbits were chosen for the experiments since in these animals the reaction of the skin to streptococcal toxin is similar to that of the human skin. Those selected were too young to have been pregnant and were isolated for at least a month before use. The toxin employed was produced in this laboratory by the Dochez N. Y. 5 strain of the *Streptococcus hemolyticus*, originally obtained from a case of scarlet fever. Toxin, heated in a boiling water-bath for two hours, and uninoculated toxin broth were used as controls to eliminate reactions which were not due to the toxic principle itself. Each rabbit received five injections: first,

a 1:1,000 dilution of broth; second, a 1:1,000 dilution of heated toxin; third, fourth, and fifth, 1:4,000, 1:2,000, and 1:1,000 dilutions of toxin (one, two, and four skin-test doses). The diluted materials were injected intracutaneously in 0.1 c.c. amounts into the animal's back after it had been denuded of hair.

The tests were read and recorded at the end of twenty-four and forty-eight hours. If the two readings did not agree, the stronger was recorded as the final result. The degree of reaction was expressed thus:

If the injection of 1 S.T.D. was followed by a reaction 10 mm.  
in diameter or greater 3+

If 2 S.T.D. caused a reaction greater than 10 mm., while the  
1 S.T.D. was less than 10 mm. 2+

If the toxin contained in 4 S.T.D. caused a reddened area at  
least 10 mm. in diameter, while the 1 or 2 S.T.D. was less +

If all the injections resulted in a visible reaction but of less  
than 10 mm. in diameter ±

No reaction -

*First Experiment.*—Twelve female rabbits were tested for skin sensitivity to streptococcal toxin at weekly intervals for nine weeks. The animals were subdivided into six groups of two animals each.

*Group 1:* Rabbits were neither immunized nor mated. While the skin of one (No. 6836) did not react to the weaker dilutions of toxin during the preliminary tests, as is frequently the case with young rabbits, it became more sensitive as the experiment progressed, and after attaining 3+ continued to give that reaction throughout the remainder of the period of observation. There was no change in the skin sensitivity of the other rabbit (No. 6843).

*Group 2:* Preliminary skin tests repeatedly gave 3+ reactions. The rabbits were then mated. Their skin reacted only to the higher concentrations of toxin during the latter part of the gestation period (see Table I). One animal failed to react to the 4 S.T.D. injection of toxin just before, and the other after, delivery. In the last test, made two weeks after delivery, the skin of both animals was still insensitive.

*Group 3:* Rabbits were immunized but not mated. After the preliminary test and at about the time the other animals were mated, the following series of subcutaneous injections of toxin was given: after an initial 4,000 S.T.D., the dose was doubled every five or six days until the fifth and last injection of 64,000 S.T.D., which was made just before the young were born. Rabbit 6839 died after the first injection of toxin and before another skin test had been done. *B. dysenteriae* Flexner was recovered from the heart's blood and was probably responsible for the death of the animal. The other rabbit (No. 6888) reacted to the smallest amount of toxin after the first two immunizing injections; after two more, 16,000 and 32,000 S.T.D., respectively, the reaction became ±; the skin failed to react to any toxin dilution after the final dose of 64,000 S.T.D.

*Group 4:* Rabbits were mated. They were then immunized with the same doses as Group 3 animals received. The skin reaction of Group 4 rabbits began to change sooner than did that of the nonpregnant immunized animal (see Table I).

*Groups 5 and 6:* Rabbits of the former group were not mated; those of the latter were. All received an intravenous dose of 0.25 c.c. of an eighteen-hour broth culture of living streptococci shortly after animals of the sixth group were mated. Unfortunately, three rabbits developed septicemia as a result of this treatment and

TABLE I. SKIN TEST FOR SUSCEPTIBILITY TO STREPTOCOCCUS TOXIN  
Comparison of Reactions in Rabbits Before, During, and After Pregnancy, With Virgin Animals

ANIMAL NUMBER	METHOD OF IMMUNIZA- TION	SKIN REACTION						REMARKS
		BEFORE* PREGNANCY	DURING PREGNANCY				POST- PARTUM†	
			FIRST WEEK	SECOND WEEK	THIRD WEEK	FOURTH WEEK		
Group 2 6889 6846		3+ 3+	3+ 3+	3+ ±	2+ -	- -		
Group 4 6834 6893	Toxin Toxin	3+ 3+	3+ 2+	+ +	- -	- -		
Group 6 6856	Culture	3+	-	D			Died following inoculation with living culture. Microscopic evidence of pregnancy. Killed to determine pregnancy. 8 dead fetuses in uterus.	
6847	Culture	3+	2+	3+	±	-	D	
Unmated Control Groups								
Group 1 6836 6843		+ 3+	3+ 3+	3+ 3+	3+ 3+	3+ 3+	3+ 3+	
Group 3 6888 6839	Toxin Toxin	3+ 3+	2+ 3+	3+ D	±			Died of intercurrent infection.
Group 5 6852	Culture	3+	3+	-	D			Died following inoculation with living culture.
6886	Culture	3+	-	-	D			Died following inoculation with living culture.

\*Average of three readings.

†Final testing two weeks after delivery.

died. While the skin reaction in all three changed, and none was elicited in the final test, it is doubtful whether any significance can be attached to these results, since the animals were moribund at the time. Rabbit 6847, one of the animals that had been mated, recovered from the inoculation. The skin of this animal became insensitive during the last week of the gestation period. She failed to deliver her young at the expected time, however, but, when she was killed, an autopsy revealed eight partially absorbed fetuses in the uterus.

*Second Experiment.*—At the termination of this experiment a second was begun. This not only served to confirm the results of the first but provided material for passive transfer and for other experiments which will be discussed later.

Five pregnant and seven nonpregnant rabbits were given skin tests at weekly intervals (see Table II). The skins of three of the five failed to react to any toxin dosage at or about the time of delivery. Only minor fluctuations were noticed in the reactions of the other two pregnant rabbits and the virgin controls.

TABLE II. SKIN TEST FOR SUSCEPTIBILITY TO STREPTOCOCCUS TOXIN  
Comparison of Reactions in Rabbits Before, During, and After Pregnancy

ANIMAL NUMBER	SKIN REACTION							
	BEFORE* PREG- NANCY	DURING PREGNANCY				DE- LIVERY	POSTPARTUM	
		FIRST WEEK	SECOND WEEK	THIRD WEEK	FOURTH WEEK		FIRST WEEK	SECOND WEEK
2006	3+	3+	3+	2+	3+	3+	2+	3+
2009	3+	3+	3+	3+	3+	3+	3+	3+
2008	3+	3+	3+	+	3+	—	2+	D
2010	3+	3+	2+	3+	3+	2+	—	3+
2012	3+	2+	+	**	3+	—	—	3+

Pregnancy With Virgin Animals

2001	3+	3+	2+	±†	3+	3+	3+‡	3+
2005	3+	3+	3+	3+	3+	3+	3+	3+
2007	3+	**	3+	3+	3+	3+	3+	3+
2013	3+	3+	3+	3+	3+	3+	2+	3+
2002	3+	2+	3+	2+	3+	3+	3+	**
2003	3+	2+	3+	3+	3+	3+	3+	3+
2004	3+	2+	3+	3+	3+	3+	3+	3+

\*Average of four readings.

\*\*Test impossible or unsatisfactory because of pigmentation of the skin.

†Reaction may have been due to position of test low on the animal's side.

‡Heated control induced a reaction nearly equal to the 1 S.T.D. of toxin.

*Testing Serum for Antitoxin.*—At this time, the three rabbits with insensitive skins were bled from the heart; the serum was separated from the clot aseptically and made up with varying amounts of physiologic salt solution and toxin to determine whether any detectable amount of antitoxin was present. Injection of the mixtures into the back of a sensitive rabbit demonstrated that no neutralization of the toxin had taken place. By the methods employed, amounts less than 0.2 of a unit of antitoxin per cubic centimeter of serum could not be detected.

*Passive Transfer of Serum.*—When no antitoxin could be demonstrated in the serum of the insensitive rabbits, 3 c.c. of serum from one was injected into a tattooed area in the back of a sensitive rabbit. Twenty-four hours later, toxin was injected into the center of this prepared area and also into a normal area outside it. Both toxin injections induced the customary reactions. A second sensitive rabbit was then prepared, with three tattooed areas on its back. One cubic centimeter of serum from an insensitive rabbit was infiltrated into the skin of the first area. Twenty-four hours later the second area and twelve hours later the third tattooed

region were similarly treated. Finally, twelve hours after the last injection of serum, toxin was injected into the center of each prepared area and into a suitable area of skin outside of them. None of these toxin injections induced reactions. When the experiment was repeated on a second sensitive rabbit with the serum from a different insensitive pregnant rabbit, the results were the same, except that the control toxin injection outside of the prepared areas showed a very slight reaction at the twenty-four-, but none at the forty-eight-hour reading.

To control these results, the experiment was repeated with the injection of normal serum from a sensitive rabbit in one animal and, in another, serum from an immunized nonpregnant rabbit with an insensitive skin. These serum injections did not influence the skin reactions in any way.

*Experiments With Follicular Hormone.*—In an effort to elucidate this phenomenon further, pseudopregnancy was induced in two rabbits by giving them gradually increasing doses of follicular hormone. After the first course of injections had been administered, the abdomen of each rabbit was opened under ether anesthesia; one horn of the uterus was removed for histologic examination, and nonabsorbable sutures were placed in the other.

The administration of the hormone was repeated every third or fourth day. The reaction of the skin to intradermal injections of toxin was determined after each dose of hormone had been given. Despite the fact that both rabbits built nests and had decidual reactions in the uterus, no alterations in the reactivity of the skin occurred.

#### DISCUSSION

Kunz and Nobel<sup>5</sup> and Burt-White and others<sup>6, 7</sup> have advocated the use of intracutaneous tests with streptococcal toxin to determine the susceptibility of pregnant women to puerperal infection. They believe that concentrated efforts can then be made to protect those who react to the toxin. While the experiments reported in this paper have not demonstrated the mechanism of the peculiar insensitivity of the skin late in pregnancy, they do indicate that intradermal tests with streptococcal toxin in gravid animals are no measure of specific immunity to this substance. They further indicate that, unless the refractory state of the skin also represents a nonspecific decrease in susceptibility to infection with the streptococcus in other tissues of the body, skin tests performed during pregnancy reveal no information of value concerning the possibilities of later infection with this microorganism. Numerous observations<sup>3, 8, 9, 10, 11</sup> on human subjects have failed to indicate that the insensitive state of the skin which occurs in some pregnancies denotes a lessened susceptibility to streptococcal infection.

#### SUMMARY AND CONCLUSIONS

Seven nonimmunized rabbits were tested for susceptibility to streptococcal toxin at weekly intervals during pregnancy. In five of these animals the skin failed to react to intradermal injections of toxin at or about the time of delivery. Antitoxin was not found in the blood, to account for this change in skin sensitivity. On the other hand, the serum of pregnant rabbits did desensitize the skin of a normally

sensitive animal when it was injected forty-eight hours before the test was performed. While these changes occurred with natural pregnancy, they were not duplicated in pseudopregnancy.

The results of this study thus suggest that some factor, or factors, other than antitoxin or the follicular hormone is responsible for the loss of reactivity to streptococcal toxin that occurs in the skin during pregnancy.

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### TRAUMATIC RUPTURE OF AN EARLY PREGNANT UTERUS

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**M**RS. F., aged nineteen, para ii, weight 90 pounds. Menstruation normal, twenty-eight-day type. Normal delivery December, 1932. The last menstrual period on Feb. 1, 1934.

The evening of June 6, 1934, Dr. G. S. Reeder found the patient suffering from intermittent pains at about five-minute intervals. There was a slight bloody, vaginal discharge. Patient was between four and five months pregnant. A diagnosis of threatened abortion was made, and morphine  $\frac{1}{4}$  gr. administered. The following morning the patient was suffering from low abdominal pains at five-minute intervals with continuance of the vaginal discharge; pulse 110, rather weak; temperature 99°; expression anxious, the pains severe and directed to the back and into both thighs. On bimanual examination the uterus was found to be about the size of a four and one-half months' pregnancy, the cervix admitted one finger easily. The lower abdomen was distended. Patient gave evidence of shock which was interpreted as due to an internal hemorrhage; probably from a ruptured extrauterine pregnancy.

Patient was transferred to the Lutheran Hospital, Fremont, Nebraska, and an abdominal section performed by Dr. C. G. Moore, shortly after admission. At the time of operation the pulse was 116 but of fair volume; temperature 99.4°, respiration 22, Hb 37 per cent, R.B.C. 3,600,000.

The abdomen contained a moderate amount of free dark, clotted blood. The fetus had escaped into the peritoneal cavity, the placenta being in the posterior culdesac. The uterus was firmly contracted and presented a rent which extended the length of the body of the uterus on the left side. A supravaginal hysterectomy was performed, and the left ovary was removed. The patient made an uneventful recovery.

*Comment.*—No myomectomy and no cesarean section had been performed prior to this pregnancy. This case is unique in that the violence done the uterus was indirect and occurred in the early months of pregnancy. It is believed that this woman received a direct blow upon her side when riding on a merry-go-round, although she was not aware of it. It seems probable that the rupture did not occur until after uterine contractions had set in; that a myometrium, infiltrated with blood, predisposed the organ to rupture when labor pains came on.

# PENTOBARBITAL SODIUM ANALGESIA\*

WITH A REPORT OF 205 CASES

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THIS report deals with a series of 205 cases in which pentobarbital sodium was used as an obstetric analgesic. At first nontoxic service cases were selected without prejudice, and later also trial labors and mild toxemias were included. Observations were made and recorded as "good," "fair," "poor," and "failures," in both objective and subjective results. No cases of what were thought to be excellent results were admitted; they were recorded as "good." Those of total failures will be discussed separately. "Good" was recorded when for objective results the patient was apparently unconscious, was cooperative, there was no delay of labor in any form, the third stage was satisfactory, and the baby did not require resuscitation. In good subjective results, the patient admitted, on questioning after delivery, a loss of pain sensibility, amounting in most cases to a total amnesia; "fair" was a somewhat lesser degree of the above; "poor" was recorded when the sum total of the effects obtained was so little better than a nonanalgesic labor that it was hardly worth while to have given the medication; "failures" were those in which there was no apparent effect from the drug.

Objective and subjective results were differentiated because we found that what was apparently a poor result objectively, in that the patient was mildly restless and complained of pain during her labor, was not a poor result subjectively, since on careful questioning later as to details, the patient had no recollection of the preceding hours. A patient who might have had a fair memory of her labor has been classified as a poor objective result, if there were a lack of cooperation, restlessness, or hemorrhage.

This investigation has demonstrated the value of satisfactory physical equipment and location of the labor room and the importance of a well-trained and cooperative nursing staff. It was observed that when patients were kept either completely or practically isolated, the results were better. It was found that those patients under the effects of the analgesic who had a minimum of external stimuli of all types, and who were spoken to or examined only when distinctly necessary (and these procedures of the utmost gentleness), had better results

\*Read at the New York Academy of Medicine, Section of Obstetrics and Gynecology, April 24, 1934.

than those for whom these factors were not considered. In some cases we were frequently met with a language difficulty, and we believe that for the best results it is important to have the ends the obstetrician is attempting to obtain, explained to, and understood by the patient. A psychic appeal should be made for her cooperation.

TABLE I

		GOOD %	FAIR %	COM- BINED %	POOR %	FAILURE %	COM- BINED %
Pentobarbital 90 multiparas	Obj.	44.4	41.1	85.5	2.3	12.2	14.5
	Subj.	26.0	56.5	82.5	3.2	14.3	17.5
Pento-Scop. 38 multiparas	Obj.	63.2	23.6	86.8	5.2	8.0	13.2
	Subj.	50.0	33.3	83.3	6.7	10.0	16.7
Pentobarbital 37 primiparas	Obj.	46.0	25.9	71.9	11.9	16.2	28.1
	Subj.	40.8	37.0	77.8	7.4	14.8	22.2
Pento-Scop. 40 primiparas	Obj.	47.5	40.0	87.5	5.0	7.5	12.5
	Subj.	38.4	53.8	92.2	3.9	3.9	7.8

These criteria are not new or unknown, but are mentioned now since they are very often overlooked, and in not infrequent instances make for the success or failure of the procedure.

We have taken "good" and "fair" as satisfactory, and "poor" as unsatisfactory results.

The figures in Table I demonstrate that pentobarbital sodium when combined with scopolamine gave better results objectively and subjectively in both multipara and primipara.

Primiparous patients gave the poorest results and the largest percentage of failures when pentobarbital sodium alone was used, and the best results when it was combined with scopolamine.

It will be observed by referring to column 3 that multiparous patients were rated slightly better objectively than subjectively, whereas primiparous patients were the reverse, giving relatively better subjective than objective results.

It is interesting to note that although the percentage of satisfactory results objectively and subjectively in the individual groups differs as much as 5.9 per cent, the total percentage of satisfactory results for all cases was 83.6 objectively and 83.7 subjectively, a difference of 0.1 per cent.

*Blood Loss.*—Blood lost was measured, not estimated. The average loss for all cases was 190 c.c. There were seven instances in which the amount exceeded 500 c.c. Of these, six had a duration of labor of from thirteen to thirty-four hours, with an average of twenty-two hours. The seventh suffered a loss of 650 c.c. of blood following a three-hour labor, during which she had been given  $4\frac{1}{2}$  gr. of pentobarbital sodium, and  $\frac{1}{200}$  gr. of scopolamine. Check-up revealed that the fundus had been permitted to fill with blood. The greatest amount of blood lost in any case



was that of a patient's losing 900 c.c., following a labor of thirty-four hours with 6 gr. of pentobarbital sodium. At the time of delivery, she was markedly exhausted.

*Time of Administration and Dosage.*—Medication was instituted when the patients were well established in labor with three- to five-minute strong pains and at least a two-finger dilatation of the cervix. Varying doses, and intervals, as well as repetitions of the drugs, were given. At the beginning small doses of pentobarbital sodium alone were used, and later, minimum doses, repeated at half-hour intervals, were administered. Toward the end of the investigation, as more knowledge was obtained, and a greater security developed, and when apparently the most satisfactory results were obtained, we were using an initial dose of  $4\frac{1}{2}$  gr. of pentobarbital sodium, with  $\frac{1}{150}$  gr. of scopolamine, given simultaneously, and the dose, in whole or in part, repeated in approximately three to four hours. The minimum amount given was  $1\frac{1}{2}$  gr. of pentobarbital sodium, and the maximum, 9 gr. of pentobarbital sodium, and  $\frac{1}{100}$  gr. of scopolamine. No toxic effects were noted with this, our largest dose. It may be well to caution, however, that no arbitrary amount of the drug, or time interval can be established. Every case should be under careful observation at all times.

*Failures.*—There were twenty-three cases of failure. Fourteen were in multiparas and nine in primiparas. In twelve of the twenty-three, we attribute the failure to the medication's having been given too late in labor, with the maximum time of forty, and the minimum time of sixteen minutes before delivery. This was obviously too short a time for full effect of the drug. Vomiting of the capsules occurred three times. One patient was given the minimum dose,  $1\frac{1}{2}$  gr. of pentobarbital sodium. Another had 3 gr. seven hours before delivery, the dose not repeated, and the effect had worn off when it was most needed. There were three instances of excitement. Besides these, there was a language difficulty with three other mothers.

We believe the last mentioned to be nonacceptable cases for analgesia because of the lack of psychic appeal.

There was no maternal mortality.

*Babies.*—There were 206 babies delivered in this series. Two hundred and one were living and breathed spontaneously. One set of premature, thirty-four-week twins required artificial resuscitation, but subsequently did well. Three babies were stillborn. The fetal heart of none of these was heard on admission of the mother to the hospital.

*Contractions.*—Contractions were found to be slowed in 4 per cent of the cases. The maximum time recorded was twenty minutes. Where a "fair" or "good" effect was obtained, it was noted that the uterine contractions continued at regular intervals and unabated strength.

*Excitement.*—Three cases of marked excitement were noted. We believe they could be physically controlled by intelligent handling on the part of the delivery room personnel. The application of delivery table accessories and administration of nitrous oxide oxygen were found to be sufficient. It has been recommended that an ampule ( $7\frac{1}{2}$  gr.) of caffeine sodium benzoate, or apomorphine in subvomiting doses ( $\frac{1}{40}$  to  $\frac{1}{16}$  gr.), be given as an antidote. Neither was used in this investigation. Of the three cases of marked excitement, one was a patient who did not speak English, and who was very apprehensive. Another was a nervous West Indian negress of low mentality. The third was a syphilitic patient who had a macerated stillborn. We would not recommend giving pentobarbital sodium to these types of patients during a subsequent labor.

*Blood Pressure.*—Blood pressure readings recorded immediately before and one-half hour after administration of the analgesic, showed comparatively little change.

The maximum recorded change was 20 systolic and 15 diastolic, about equally divided between rise and fall. There was no case of shock.

*Subsequent Anesthesia.*—Final anesthesia was given in about 50 per cent of the cases by internes, and in the other half by the resident anesthetist of the hospital. She has reported all pentobarbital sodium cases as using less anesthetic than the others, and more than half of these, about 25 per cent of the total number of patients, needing little or no ether at the end of the second stage. Recovery immediately postpartum was found to be uneventful. There was no case of marked respiratory infection.

*Operative Incidence* for all ward deliveries at this hospital over the same period of time was 19.1 per cent. The operative incidence for this series was 16.1 per cent. Neither includes cesarean sections. This shows a slight lowering of the operative interference, following the exhibition of these drugs.

#### SUMMARY

There was no maternal mortality. There was no fetal mortality that could be attributable to the drug. Labor was not inhibited for any appreciable time, and delivery anesthetic was reduced. The third stage of labor was without untoward incident, and postpartum recovery was uneventful. Blood loss was within normal limits, and blood pressure was not appreciably affected. Excitement occurred infrequently and was controllable. The combination of pentobarbital sodium with scopolamine proved more effectual than the former alone.

#### CONCLUSIONS

1. Medication should be given early to be effective. The patient should be definitely in labor, the cervix thin, and one to one and one-half fingers dilated, and the dose repeated in whole or in part if necessary.

2. All external stimuli should be avoided.

3. The complete cooperation of a well-trained assisting staff is important.

4. This drug should be administered only to carefully selected patients.

5. Sufficient medication is necessary, and careful observation of the patient is essential.

6. The limits of the investigation have confirmed the original premise, i. e., safety for mother and child.

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Vallebona, A., and Giavotto, G.: Therapy with Short Wave Length Diathermy in Pelvic Inflammatory Disease in Women, *Folia gynec-demograf.* 31: 207, 1934.

The authors used diathermy of 200 meters instead of the usual 500-600 meters diathermy wave lengths. In 30 cases they found inflammatory processes greatly benefited.

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# AN ANALYSIS OF MATERNAL MORTALITY IN TEN THOUSAND OBSTETRIC CASES

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THIS presentation is a detailed study of the maternal mortality of 10,000 consecutive obstetric cases treated at the Israel Zion Hospital from 1923 to 1932. It is a portion of a comprehensive survey of a cross-section of obstetrics as observed and managed in a general hospital with a large visiting staff participating in the same. The purpose of this paper is not merely to review the mortality statistics of an obstetric service but to analyze each death as to whether or not it was preventable. Thus, an attempt is made to ascertain the factors responsible for the fatality and to point out in each instance what can be learned concerning the proper management of a similar case.

No paper of this type can possibly fail to call attention to the recently issued report of the New York Academy of Medicine Committee on Maternal Mortality.<sup>1</sup> Their appalling conclusion that 65.8 per cent of 2,041 maternal deaths were preventable should make us pause and take stock of our *modus operandi*. In this paper we report 36 maternal deaths, which is a rate of 3.6 per thousand, or 0.36 per cent. Of these, 17 occurred in primiparas and 19 in multiparas. Eight multiparas were para i, 5 were para ii, 3 were para iii, 2 were para iv, and 1 was para ix.

The method of delivery and operative procedures were as follows:

Undelivered	10	3 primiparas and 7 multiparas
Spontaneous deliveries	14	6 primiparas and 8 multiparas
Low forceps	2	1 primipara and 1 multipara
Midforceps		1 primipara
Incision of cervix and forceps		1 primipara
Two-forceps maneuver		1 primipara
Version and extraction		1 primipara
Version and craniotomy		1 primipara
Porro cesarean section		1 multipara
Classical cesarean section		1 primipara
Low cervical 2-flap section	3	2 primiparas and 1 multipara

The causes of death were as follows: Sepsis 10, hemorrhage 5, eclampsia 5, cardiac 4, pneumonia 3, embolus 3, ruptured uterus 2, preeclamptic toxemia 1, tuberculosis 1, diabetes 1, and spinal anesthesia 1.

AN ANALYSIS OF THE MATERNAL MORTALITY ACCORDING TO  
OPERATIVE PROCEDURE

In 10,000 cases there was operative interference in 1,621, an incidence of 16.2 per cent. Operative procedure was done in only 12 of the 36 maternal deaths. If we may disregard causes of death and associated complications, in 1,621 instances of operative interference there were 12 fatalities or an incidence of 0.75 per cent. The operative procedures are as follows:

*Forceps.*—Low forceps constituted 75 per cent among 3,110 instrumental deliveries; the balance was midforceps, with the exception of 4 high forceps dating back to the beginning of this series, before this procedure was abandoned in favor of version or cesarean section. Uterine inertia and fetal distress were the indications for over half of the total number. Concerning the latter, a drop in rate and an irregularity in rhythm were considered of more significance than an increase in rate. Forceps delivery was necessary 3 times more frequently in primiparas than in multiparas. The gross fetal mortality incident to forceps delivery was 5 per cent, with the duration of labor obviously a potent factor in increasing the same. Routine episiotomy was practiced in primiparas. There were 5 mortalities, one a bad cardiac, one sudden death proved at autopsy to be pulmonary embolus, two deaths were due to sepsis, and one to a ruptured uterus, the result of the two-forceps maneuver in inexperienced hands.

*Breech Extraction.*—Breech extraction occurred 96 times with a fetal mortality of 20, an incidence of 20.8 per cent. There were no maternal deaths in this group. In the absence of any urgent indication for hastening the delivery we have not favored "breaking up the breech," but have permitted it to deliver as such.

*Version and Extraction.*—Version and extraction was performed 72 times, with a fetal mortality of 25 per cent and one maternal death in a case of placenta previa.

*Cesarean Section.*—There was a total of 129 cases, an incidence of 1.29 per cent, with 5 deaths, a mortality ratio of 3.92 per cent. Contracted pelvis were the indication in 60 per cent of all cases; 24 were done for cardiac decompensation, 17 for disproportion, 8 for placenta previa, 5 for eclampsia, and 6 for preeclamptic toxemia. The classic operation was performed on all elective cases, the low 2-flap operation on all patients in labor or with ruptured membranes. There was some type of morbidity present in 37 per cent of all classic sections as compared to 32 per cent in all the low cervical cases. However, it must be kept in mind that every patient in the latter group was given a trial test of labor. The morbidity rate increased in direct proportion to the time interval between the operation and the onset of labor plus ruptured membranes as shown so well in the survey of C. A. Gordon.<sup>2</sup>

Of the 5 deaths in this group, one could not be charged to the operative procedure. This occurred as a result of spontaneous rupture of the uterus in a para ix, ten hours in labor, who reached the operating table in a moribund condition. Of the remaining four deaths, two were due to pneumonia and two to sepsis. These latter two mortalities will be discussed under puerperal sepsis.

## PUERPERAL SEPSIS

Among 36 deaths, there were 10 fatalities from puerperal sepsis, 7 in primiparas. This we attribute to the greater frequency of toxemia, protracted labors and need for operative interference in patients of this parity.

*Prenatal Care.*—Two of our 10 fatal cases of sepsis had well-marked toxemias of pregnancy on admission, while four others were observed to have had albuminuria ranging from 1+ to 3+. In two instances in which fatal sepsis occurred, no factor could be held responsible other than coitus within a day prior to rupture of the membranes. Examination of the male prepuce is mentioned by Irving<sup>3</sup> as showing streptococci in about 75 per cent of the cases. Further, more emphasis should be laid on the necessity for reporting rupture of the membranes without the onset of pains. In two instances there was rupture of the membranes three days before the patient applied for admission and in one of these instances the patient had a temperature of 100.6° F. on admission. In this latter case, in spite of a rapid spontaneous delivery, the patient succumbed to puerperal sepsis. In the first case, because of obstructive dystocia, a low 2-flap cesarean section was performed. There is a question whether a Porro hysterectomy might not have saved this patient from a fatal sepsis.

The New York Academy of Medicine Committee on Maternal Mortality has shown puerperal sepsis to be five times as frequent following operative interference as compared with spontaneous delivery. In our ten deaths from sepsis, four patients had prolonged labors and five operative interferences with anesthesia. Adequate prenatal investigation should reduce the incidence of prolonged labors and diminish thereby the risk attendant to operative procedures.

*Endogenous Infections.*—Two of our women upon whom vaginal examinations had not been made during labor and who had been delivered spontaneously and quickly with the most approved aseptic technic, developed fatal puerperal sepsis. One of the patients was admitted with the caput slightly visible and protected by membranes. She developed a fatal peritonitis and hemolytic streptococci were cultured from the peritoneal fluid.

*Causative Organisms.*—In our 10 deaths, the blood culture was positive for hemolytic streptococci in three cases, for staphylococci in one case, for *B. coli* in one case, and for *B. welchii* in one case. Two cases had repeatedly negative blood cultures and in two cases blood cultures were not taken. In spite of the near proximity of the rectum to the internal genitalia, it is most unusual for puerperal sepsis to be caused by the gas bacillus.

Our fatal case of Welch Bacillus infection gave the following history: A forty-two-year-old para iii was admitted in premature labor with the membranes already ruptured. An amputation of the cervix had been done seven years previously. On physical examination the temperature, pulse, and respiration were normal. The cervix could not be felt on vaginal examination or seen on inspection with a speculum. Irregular pains were present on admission and continued for three days. On the third day there was a rise in temperature to 100°. Because of the presence of infection, operative interference was deemed contraindicated. On the following day the patient suffered a chill and a temperature of 102°. At this time the blood culture was positive for *B. welchii* and on this day she delivered spontaneously a premature stillborn fetus. The placenta could not be expressed. Eight hours postpartum a hysterectomy was performed for the purpose of removing the focus of infection feeding the organisms to the blood stream. Acriflavine and perfringens antitoxin were administered intravenously. She died on the sixth day postpartum. On histologic examination the extirpated uterus showed a septic metritis.

#### TOXEMIAS OF PREGNANCY

*Preclampsic Toxemia.*—There was one maternal death, due apparently to the toxemia.

*Eclampsia.*—There were 58 eclampsies, of whom 34 were antepartum, 10 intrapartum and 14 postpartum. Among these, there were 4 antepartum and 1 intra-

partum deaths. All of the postpartum cases recovered. In this group 44 patients gave a negative history, 7 had a preexisting nephritis, 5 had toxemias in previous pregnancies. Thirty-five had had prenatal care, and 23 had no prenatal care. The treatment was expectant in all cases, with the exception of 4 patients who did not respond to medical therapy; these were terminated by abdominal delivery under local anesthesia. There were 26 stillbirths in this group. As noted above, 5 deaths occurred in 58 cases, or an incidence of 9 per cent. This compares favorably with the incidence of death in eclampsia by other authors and argues well for the conservative medical treatment which we have adopted as our routine in the treatment of this condition. In our experience, the intravenous administration of glucose, the intramuscular injection of morphine and magnesium sulphate have proved of unquestionable value.

The consideration of our five fatal cases as a group brings forth several points of interest.

1. *The High Incidence of Low Parity.*—Three of the deaths were in primiparas and two in para i, but this is merely a part of the high incidence of low parity for all cases. Thus 30 of our 58 cases were primiparas.

2. *The Prognosis Is Dependent Upon the Number of Convulsions and Their Time of Occurrence.*—In each instance in our series in which death occurred, the patient was admitted to the hospital after four or more convulsions had taken place. In 14 instances of postpartum eclampsia there were no deaths.

3. *The Importance of Prenatal Care in Prophylaxis.*—This is by far the most important point to emphasize. None of the 5 patients who died in this series received adequate prenatal care.

#### POSTPARTUM HEMORRHAGE

So far as maternal mortality is concerned, the third stage of labor is considered by many obstetricians to be the most dangerous, and mainly because of the frequency and seriousness of severe postpartum hemorrhage. It occurs about once in 100 cases, 95 times in our series of 10,000 cases. It is the most common cause of maternal death and it is generally conceded that more women die of postpartum hemorrhage than from placenta previa and premature separation of the placenta together. Yet in our series, we had but one death from this complication, although we have had four deaths from placenta previa and premature separation of the placenta.

#### RUPTURED UTERI

Two of the cases of ruptured uteri resulted fatally.

CASE 1.—This patient was a twenty-five-year-old primipara who had been in labor forty-three hours. There was a well-marked contraction ring. A two-forceps maneuver was attempted by an inexperienced operator. The patient went into shock and died forty-five minutes later. Death was due to rupture of the uterus. This fatality was preventable and was due obviously to the inexperience of the operator. It should serve to show that only adequate supervision of the work of the house staff by a capable attending staff can prevent a similar tragedy.

CASE 2.—The patient was a forty-four-year-old para ix, who had a vertex presentation; she had had ten hours of moderate labor pains and was 3 fingers dilated. For no apparent reason she suddenly became pulseless and went into extreme shock. The abdomen was rigid. No pituitary extract had been given. An immediate laparotomy revealed a rupture of the uterus at the cervicovaginal junction extending into the broad ligament. She died on the operating table. Microscopic examination of the uterus after removal showed leucocytic infiltration in the area of rupture.

In this last case, the complication occurred in a patient who was under observation in a hospital where all the facilities necessary for rapid treatment were available and yet death resulted. Transfusion and rapid laparotomy with hemostasis and repair, or hysterectomy, with little regard for the toilet of the operation, may save what appears to be a moribund patient.

#### PLACENTA PREVIA

Of 57 cases, 39 were of the marginal type, 11 partial, and 7 total. Of these, 8 were terminated by cesarean section. In the remainder, the bleeding was controlled by vaginal packing or Pomeroy bag followed by Braxton-Hicks version. Postpartum febrile morbidity occurred in 11 cases, of which 7 had vaginal packing prior to admission to the hospital. There were three maternal deaths. Two patients died of hemorrhage undelivered. In one of these patients transfusion might have saved the patient. She was a twenty-two-year-old primipara who was admitted because of irregular pains in the sixth month of gestation. There was no dilatation of the cervix and no bleeding at this time. Twelve hours after admission the patient suddenly suffered a severe hemorrhage. Vaginal examination showed the cervix to be 2 fingers dilated and a partial placenta previa. A second severe hemorrhage occurred and the patient died eighteen hours after admission.

This case illustrates the danger of a vaginal examination unless the examiner is prepared to treat the patient for placenta previa, as this procedure commonly precipitates a severe hemorrhage. In the face of one severe hemorrhage a compatible donor should have been secured and a transfusion given before attempting vaginal examination.

The third death occurred in a patient who died suddenly one hour postpartum, presumably of an embolus. This case also must be discussed more fully, for there is danger in the handling of such a patient that must not be disregarded. The case history will be found in the section on pulmonary embolism.

We have been favorably inclined toward the recent trend of abdominal delivery in all cases of the totalis type and selected cases of the partialis type.

#### PREMATURE SEPARATION OF THE PLACENTA

There were 18 cases, of which 4 were of the severe type, as manifested by extreme shock and anemia, 3 were moderately severe and 11 were of the mild type. Nine patients were treated expectantly, three had a bag induction and delivered spontaneously, one was terminated by forceps, one by breech extraction, one by version and breech extraction, and two by abdominal route.

There were two maternal deaths, an incidence of 11.1 per cent. One woman died undelivered. She was admitted to the hospital in a grave condition, following one week of pain accompanied by constant oozing. Autopsy revealed partial separation of the placenta. The second fatal case was that of a para ii who was admitted in shock and showed no external bleeding. The uterus was spastic and tender. The membranes were ruptured artificially, and there was moderate bleeding as a result. After four hours of labor she spontaneously delivered an eight-month fetus. Following spontaneous delivery of the placenta, the patient had a profuse uncontrollable hemorrhage and died. In retrospect, this case could have been better controlled by immediate abdominal delivery.

#### PULMONARY EMBOLISM

There were three maternal deaths from this complication. The factors that may have been responsible for the three fatalities from this tragic accident differ widely. One death occurred in a twenty-two-year-old primipara who, after forty hours of

labor, was delivered by midforceps. Following a manual removal of the placenta the patient suddenly went into shock and died. The case reports of the remaining two deaths will be presented in some detail, and will emphasize, in part, the prophylaxis of pulmonary embolus.

CASE 1.—H. H., twenty-nine years old, para i, at term, was admitted in labor. The blood pressure was 120/90, and albuminuria was absent. There was a cysto-rectocele and bilateral laceration of the cervix. After six hours of labor she was delivered spontaneously of a normal infant. On the seventh day postpartum the uterus was found to be two fingers above the symphysis pubis, there was a slight serosanguineous lochia and the general condition of the patient was good. The puerperium up to this period had been afebrile. Under spinal anesthesia an anterior colporrhaphy, posterior colporrhaphy, and trachelorrhaphy were performed. The patient was returned to her bed in good condition. Eleven hours postoperative, the patient was restless and vomited. The temperature was 100.4°, the pulse 114, the respiration 22. It was felt that the patient was experiencing a customary post-operative reaction. Three and one-half hours later she was found dead in bed. The house doctor noted that this was the most sudden unexpected death he had ever witnessed.

CASE 2.—M. B., a twenty-year-old primipara, at term, was admitted with the history that she had been in labor for several hours. She had been attended by a midwife who became alarmed by a profuse hemorrhage and called an ambulance. When first seen on admission she complained of nausea, headache, and weakness. She was pale, dyspneic and slightly cyanotic. The pulse was rapid and thready and the extremities cold. The blood pressure was 95/50, and the hemoglobin 32 per cent. There were occasional uterine contractions. The fetal heart sounds were faint, the rate about 100. On rectal examination the cervix was felt to be soft and no dilatation could be made out. The presenting part could not be felt and a soft boggy mass was palpated. A diagnosis of placenta previa centralis was made and the patient observed for about eighteen hours. During this period, therapy included digifolin and morphine by hypodermic, but no transfusion or intravenous infusions.

A version was finally decided upon and under general anesthesia both feet were brought down. The patient was then allowed to come out of the anesthesia and deliver herself spontaneously in one-half hour. The hemoglobin was 25 per cent after delivery. Although the patient's general condition was considered poor, it was not alarming. On being moved from the delivery table on to a stretcher soon after delivery, the patient suddenly became more cyanotic, suffered a generalized seizure and died. The object lessons to be learned from this case are the following:

1. In the face of a history of a severe hemorrhage and a patient showing the signs of an acute anemia, a transfusion obviously should have been given soon after admission.

2. It is our impression that the actual cause of death was pulmonary embolus precipitated by moving the patient too soon after delivery in a case of placenta previa. With this condition there must be even greater engorgement in the pelvis than occurs with a normal implantation of the placenta. Since this particular tragic accident occurred we have been careful to adhere to the rule of allowing the patient to remain for at least one hour on the table following this type of delivery.

3. With a central placenta previa in a primipara, a cesarean section should be the treatment of choice.

#### CARDIAC DISEASE

We had 70 cases of cardiac disease, 6 of the patients were decompensated; 21 were delivered spontaneously, 4 by cesarean section, 1 by breech extraction and the largest



number, 42, by forceps. Two remained undelivered. There were 4 deaths due to this complication. Since such deaths occur in nongravid, this is not a high incidence for a series of 10,000 cases. Three patients were para ii and one was a primipara. Their ages ranged from twenty-one to forty-two years. One patient died before delivery, 2 within six hours after delivery, and 1 on the third day postpartum.

It is noteworthy that three patients died soon after admission to the hospital. This must mean inadequate prenatal care. A cardiac who becomes gravid must be observed carefully during the entire length of gestation for any indication of impending decompensation and then promptly hospitalized.

#### MISCELLANEOUS CAUSES OF DEATH

1. *Pneumonia*.—There were 4 deaths due to pneumonia, two of the lobar type and one of these was further complicated by diabetes. The remaining two deaths were of the bronchopneumonia type and occurred after cesarean section.

2. *Tuberculosis*.—There were five cases of pulmonary tuberculosis in the entire series. Three patients were delivered spontaneously and two by low forceps. One of the patients delivered spontaneously died of miliary tuberculosis.

3. *Diabetes*.—There were nine cases of diabetes in the entire series. One patient was delivered spontaneously and eight by operative procedures. In one death diabetes complicated a lobar pneumonia. This case has been mentioned above.

4. *Spinal Anesthesia*.—There was one death wholly from this cause. It occurred in a patient who was being anesthetized for a cesarean section. Since the recent trend of accepted opinion that the risk attendant to spinal anesthesia is of major proportions, we have discontinued its use, except in definitely selected cases.

The compilation of these data was completed with the assistance of Dr. Elmer Gergely and Dr. Aaron J. Orloff and credit is gratefully acknowledged. I am likewise indebted to Dr. Leo Schwartz, Chief of Service, for the privilege of reporting this material and for his generous cooperation in the final preparation of this paper.

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In spite of improved prenatal care, reliable statistics prove that the maternal mortality rate has not been decreased, because the good work of the trained and skilled physician is overbalanced by the poor work of the unskilled and unscrupulous practitioner. It is the duty of every physician to help improve the maternal mortality rate by educating the laity to demand better obstetrics.

J. THORNWELL WITHERSPOON.

## THE DETERMINATION OF URINARY HISTIDINE AS A CHEMICAL TEST FOR PREGNANCY

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IN 1929 Voge<sup>1</sup> described a chemical test for pregnancy based on Knoop's test for histidine, performed simply by boiling urine with bromine water, which, in a small series of 60 cases, gave a 95 per cent correlation with the Aschheim-Zondek test.

The accuracy of this test would appear to have been amply disproved by the work of later investigators<sup>2, 3, 4</sup> who, with much larger series, found only 63 to 75 per cent positives in pregnancy, with from 8 to 16 per cent of false positives among the controls.

However, Knoop's test for histidine, as applied to urine, is far from satisfactory. The color change is usually by no means striking, and its intensity depends upon the general composition of the urine, rather than upon its histidine content alone. Some urines give an intense reaction with histidine concentrations of less than 1:20,000, whereas others may show a scarcely detectable change with histidine concentrations over 1:5,000.

In view of the fact that histidine, in small amounts, is a normal constituent of urine, it was felt that such a qualitative test could never determine the ultimate value of histidine excretion as the basis for a pregnancy test. Therefore it seemed worth while to run a series of cases, using a procedure which should be at least roughly quantitative.

During the pursuit of this investigation interesting questions arose as to the possible significance of this phenomenon. These cannot be answered in the present paper, which deals only with the practical aspect of the problem.

*Experimental.*—The method of determining histidine employed in this series is a simplification of that described by Kappel-Adler.<sup>5</sup> Reagents necessary are:

- (1) Hopkins' reagent (a solution of 10 per cent mercuric sulphate in 5 per cent  $\text{H}_2\text{SO}_4$ ).
- (2) A solution of 2 parts concentrated  $\text{NH}_4\text{OH}$  and 1 part 10 per cent  $(\text{NH}_4)_2\text{CO}_3$ .
- (3) A solution of 1 per cent bromine in 33 per cent acetic acid.

Ten cubic centimeters of urine are transferred into a 15 c.c. centrifuge tube, and the remainder of the tube filled with Hopkins' reagent. The precipitate is spun down and the supernatant fluid poured off. Enough distilled water is added to bring the total volume up to 2 or 3 c.c. The precipitate is then decomposed with  $\text{H}_2\text{S}$ , agitating with a stirring rod until a uniform inky black suspension is obtained. The

precipitated mercuric sulphide is spun down and the clear, colorless or yellow fluid is poured off into a clean graduated tube. The  $H_2S$  is expelled by bubbling air vigorously through the solution for about thirty seconds. The bromine is then added drop by drop until the solution remains bright yellow. Frequently the solution first becomes pinkish and then yellow upon further addition of bromine. After ten minutes 2 c.c. of the ammonia mixture are added and the solution heated for one minute on the boiling water-bath. The solution is cooled, made up to 10 c.c. volume, and the color, ranging from a light pink to a deep purple, is compared in the colorimeter with the color developed by 1 c.c. of a standard solution containing 1 mg. of histidine. The comparison should be made without delay, as in some urines the color fades rapidly.

The precipitation of histidine by Hopkins' reagent appears to be partially a "dragging down" effect. Histidine cannot be satisfactorily recovered in this fashion from pure water solution or from urine which is too dilute to yield 0.5 c.c. of precipitate (below sp. gr. 1.012). Too concentrated urines should be diluted before analysis because of the intensity of the interfering brownish color which otherwise develops. The presence of large amounts of albumin or salicylates render the determination unsatisfactory by preventing the bromination of histidine.

No claims are made for this procedure as an accurate analytical method. Colors developed in urine seldom compare exactly with the standard because of the admixture of a yellowish tinge. Recoveries from concentrations above 1:20,000 vary from 80 per cent to 100 per cent. However, any more exact method would be much more laborious, and under the conditions of the experiment, could add little to the significance of the results.

Samples were taken from specimens collected routinely on the wards or in the outpatient departments of the hospital. Specimens obviously too dilute were either discarded or subjected to preliminary concentration on the steam bath. The least readily detectable amount of histidine was considered to be 5 mg. per cent since colorimetric readings below this figure are not significant.

Determinations were made upon specimens from 199 female subjects: 102 pregnant and 97 nonpregnant. In the pregnant group 94 were positive and 8 were negative. In the nonpregnant group, 24 were positive and 73 negative. Thus the test was positive in 92 per cent of pregnancies but yielded 25 per cent of false positives. That the accuracy of the test cannot be improved by setting up any arbitrary level of histidine concentration as significant, is shown in Table I.

TABLE I

Minimum conc. of histidine	50 mg. %	40 mg. %	30 mg. %	20 mg. %	10 mg. %	5 mg. %
Pregnant	6	10	15	34	73	94
Nonpregnant	0	0	1	3	10	24

The quantities of histidine excreted bore no evident relationship to the duration of the pregnancy. Two negatives were obtained during the first trimester, three during the second, and the other three at term. The earliest positive result obtained was at six or eight weeks. The unusually high levels of histidine excretion were found scattered throughout the period of gestation. Only two patients were followed after parturition. They were still positive at two weeks and were negative at three weeks.

The controls used in this series were not normal, but included the general run of the wards and clinics, selected only in regard to child-bearing age. Positive results were obtained in 4 out of 6 cases of pelvic infection, 2 out of 4 myomas, and 3 out of 9 postoperative cases. However, positive results were also obtained in 7 out of

15 cases whose complaints had to be classified as "functional." The other positive results represented as many different types of disease. Ovulation tests were carried out whenever there appeared to be the slightest possibility of pregnancy.

As a matter of curiosity, determinations were made upon a few male specimens, with the interesting result that considerable quantities of histidine were found in 3 out of 4 cases of undescended testicles. Ovulation tests performed with 2 of these specimens were negative.

#### DISCUSSION

It is obvious from the above experiments that the quantity of histidine in a single urine specimen cannot serve as the basis for a satisfactory pregnancy test. Whether or not more striking differences might be demonstrated by histidine balance studies over extended periods, is of theoretical interest only, since the test would then become too cumbersome to replace the highly successful rabbit ovulation test.

Little is known of the metabolism of histidine, and no explanation can be offered for its increased excretion in the urine. That this is in some way influenced by the sex hormones is apparent from its high association with pregnancy in the female, and with undescended testicles in the male. It is equally apparent from the negative ovulation tests obtained with urines of high histidine content, that histidine is not necessarily excreted in any intimate relation to the hormones of pregnancy.

#### CONCLUSION

The excretion of histidine in the urine merits further study as an interesting biochemic phenomenon, peculiarly characteristic of the pregnant state. However, it is not specific enough to serve as the basis for a reliable pregnancy test.

The author wishes to express his thanks to Dr. C. A. Elden for aid and encouragement in this work.

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Holzapfel, K.: The Treatment of Climacteric Bleeding With Vaporization, Monatschr. f. Geburtsh. u. Gynäk. 97: 269, 1934.

In the treatment of climacteric hemorrhage there are five measures which may be used, namely, medical and endocrine therapy, curettement, vaporization, irradiation and extirpation of the uterus. In most cases, especially the mild ones, medical and endocrine therapy are employed. If no relief is obtained, the suspicion of carcinoma is aroused and a curettement is performed. In most instances, however, this operation is not curative and thus the choice lies between vaporization, irradiation and removal of the uterus. The last is the most radical whereas vaporization is the simplest. Holzapfel has employed vaporization 111 times in the last thirty-two years, and among these cases he encountered two fatalities. He describes the technic he employs.

J. P. GREENHILL.

## ANALYSIS OF ONE HUNDRED AND FORTY-SIX CASES OF PLACENTA PREVIA\*

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*(From the Clinic of New York Nursery and Child's Hospital)*

LAWSON TAIT in 1899 advocated cesarean section for placenta previa. This radical departure aroused a violent storm of criticism and opposition from a conservative profession. Even today, there is great reluctance to accept this procedure in such celebrated centers of midwifery as the Rotunda, in Dublin, and Queen Charlotte's, in London. But a more surgically minded generation has accepted Tait's innovation which has gradually won itself a place in the treatment of an obstetric complication where both mother and child are in serious jeopardy. In 1931, Bill of the Cleveland Maternity Hospital published his series of 104 placenta previas, 79 per cent treated by cesarean section showing the lowest maternal and fetal mortality of any large series. This led me to review the cases of placenta previa treated at the New York Nursery and Child's Hospital, in hope that some light might be thrown on the relative values of the different methods of treatment, especially as the work of many operators would subject any one maneuver to a critical test.

The following report is based on a study of one hundred and forty-six patients with placenta previa which occurred during the past fifteen years, from 1918 to 1932 inclusive. The incidence of frequency of this complication was one in 278 patients which corresponds closely with other published reports of hospital series. On the basis of the recognized divisions of placenta previa, there occurred in this series, 32 central, 39 lateral, and 75 marginal placenta previas.

### METHOD OF DELIVERY IN CENTRAL PLACENTA PREVIA

Of the 32 patients presenting central placenta previa, 19 (15 per cent were subjected to cesarean section with no maternal mortality and 21 per cent fetal mortality. Of these 6 had occurred in primiparas and 13 in multiparas. Five patients (15 per cent) were subjected to bagging, followed by internal podic version, with no maternal mortality and 40 per cent fetal mortality. Two patients were subjected to an internal podalic version with one maternal death (50 per cent) and 100 per cent fetal mortality. Two patients were subjected to bagging, accouchement forcé and followed by a breech extraction, with one maternal death (50 per cent) and 100 per cent fetal mortality. One patient was subjected to bagging, and followed by a

\*Read before the Medical Society of the County of New York, April 27, 1934.

breech extraction with one fetal death. One patient was subjected to bagging, accouchement forcé followed by a version, the patient and child survived. Two patients were subjected to accouchement forcé and version, with no maternal mortality and one (50 per cent) fetal mortality.

#### METHOD OF DELIVERY IN LATERAL PLACENTA PREVIA

There were 39 patients presenting lateral placenta previa with no maternal deaths. Of these, three were treated by cesarean section, two were primiparas and one was a multipara. Six patients were subjected to bagging, followed by an internal podalic version, with a fetal mortality of 83 per cent. Six patients were subjected to bagging, followed by forceps, with a fetal mortality of 16 per cent. In 16 patients the membranes were ruptured artificially, followed by a normal delivery or forceps, with 3 fetal deaths. Four patients were subjected to an internal podalic version, with 4 fetal deaths. Two patients were subjected to accouchement forcé and forceps, with one (50 per cent) fetal death. Two patients were subjected to bagging and followed by normal delivery, both babies died.

#### METHOD OF DELIVERY IN MARGINAL PLACENTA PREVIA

There were 75 patients, presenting marginal placenta previas with 5 maternal deaths. Of these, 18 patients (24 per cent) were subjected to cesarean section, one mother died on the eighth postoperative day, following a transfusion, giving a maternal mortality of 5 per cent and fetal mortality of 20 per cent. Thirteen of these were primiparas and 5 multiparas. Twenty-one patients were subjected to bagging, followed by internal podalic version with one maternal death (4.7 per cent) and 52 per cent fetal mortality. Fifteen patients were subjected to simple rupturing of the membranes or combined with forceps, with no maternal mortality but 50 per cent fetal mortality. Five patients were subjected to bagging, followed by forceps with one maternal death and one fetal death. Five patients were subjected to accouchement forcé and forceps, or internal podalic version with 2 maternal deaths and 3 fetal deaths. Four patients were subjected to an internal podalic version, with no maternal deaths and one fetal death. One patient received a Braxton Hicks version; the mother lived, the fetus died.

There were a total of 40 cesarean sections in this series which included thirty-two classical operations, three low flaps, two peritoneal exclusions, one Porro and two vaginal hysterotomies. The vaginal hysterotomies were performed on primiparas, one at term, one at the twenty-seventh week, both were of the marginal type.

There was one maternal death in this group of 40 cesarean sections, but it cannot be attributed to the operation, rather to the incompatible blood administered on the eighth postoperative day. Assuming that cesarean section is a radical procedure, it carried the least maternal mortality and the least fetal mortality. On the other hand the conservative method was employed on 32 occasions in which the membranes were ruptured artificially, followed by a spontaneous delivery or by forceps. There was no maternal mortality but the fetal mortality was 37.5 per cent.

Between these two groups, the one treated by cesarean section, the other, conservatively, there was an intermediate group, consisting of 73 patients, which were treated rather vigorously. Twelve patients received accouchement forcé with 3 maternal deaths (25 per cent) and 6 fetal deaths. In 50 instances the bag was the initial procedure followed by version or forceps, with two maternal deaths (4 per cent) and 25 fetal deaths. Ten patients were subjected to internal podalic version, with one maternal death (1 per cent) and a fetal mortality of 70 per cent. One Braxton Hicks version was performed, the mother survived, the fetus was stillborn.

## ANALYSIS OF MATERNAL DEATHS

A brief review of the fatalities reveals that five patients died before leaving the operating room of a combination of hemorrhage and shock. One patient died immediately on receiving incompatible blood on the eighth day and one patient died of sepsis on the thirty-first day. All these patients entered the hospital in good general condition; by that is meant, they were not exsanguinated or infected from previous vaginal manipulations.

A. R., para i, aged twenty-two, at term, vertex, marginal previa, low classical cesarean section, received a transfusion immediately following delivery. On the eighth day, a second transfusion proved fatal due to incompatibility.

M. G., para vi, aged thirty-five, eight months, vertex, central previa, was three fingers dilated, soft, thin, bleeding briskly, received accouchement forcé and internal podalic version. Ran a definite septic course and died on the thirty-first day postpartum.

M. Q., para i, aged thirty-five, at term, vertex, marginal previa, three-finger dilatation, a No. 4 bag inserted, followed by forceps after a long hard labor. Bled profusely following delivery, was packed and repacked, transfused but died in operating room of hemorrhagic shock.

D. G., para i, aged thirty-three, seven and one-half months, breech, central previa, two-finger dilatation, a No. 4 bag inserted followed by a breech extraction, bleeding profusely, packed, infused but died in operating room of hemorrhagic shock.

D., para i, aged thirty-six, nine months, vertex, three-finger dilatation, marginal or low implantation. Slowing fetal heart, the cervix was incised anteriorly and followed by forceps. The patient died just as transfusion was started; cause, hemorrhagic shock.

H., para ii, aged thirty-one, eight and one-half months, vertex, marginal previa, two-finger dilatation, a No. 4 bag and followed by internal podalic version, bleeding profusely, packed, transfused and infused. Died shortly of hemorrhagic shock.

W., para iv, aged thirty-six, nine months, vertex, almost fully dilated, received internal podalic version with laceration of cervix extending into broad ligament and died in operating room of hemorrhagic shock.

## SUMMARY

In this series of 146 patients with placenta previa in 33,464 deliveries, or an incidence of one in 278 patients, there were 56 primiparas and 90 multiparas. Bleeding occurred at term in 71 patients. Uterine and vaginal packing postpartum was deemed necessary in 60 patients (41 per cent). Of the 40 cesarean sections, 16 received uterine packing following removal of the placenta. Transfusion was performed on 31 occasions, twelve patients were transfused antepartum.

There were 7 maternal deaths (4.7 per cent). Five patients died of hemorrhagic shock. One patient died of sepsis and one patient died following a transfusion of incompatible blood. The uncorrected fetal mortality was 53 per cent.

A significant fact is that the maternal mortality from central placenta previa and marginal placenta previa is 6.2 per cent and 6.6 per cent respectively.

The maternal mortality in cesarean section is 2.5 per cent in contrast to 5.6 per cent in delivery by vaginal route.

The fetal mortality is 20 per cent by cesarean operation and 49 per cent by the vaginal methods.

#### CONCLUSIONS

Rapid dilatation of the cervix with immediate extraction of the fetus, i.e., accouchement forcé, is an unwise and unsatisfactory procedure. No matter what the disguise, it is a maneuver which should be unreservedly condemned.

The intrauterine bag produces results similar to those following accouchement forcé, these bad results are due to the blood loss before bagging, the trauma at insertion, and last, and of greatest importance, the considerable postpartum hemorrhage.

There are selected cases of marginal placenta previa, with adequate dilatation of the os, and engagement of the head, where artificial rupture of the membranes, with forceps delivery, is safe for the mother but entails a high fetal mortality. Under the same conditions, internal podalic version can be employed for an unengaged head with the knowledge that the fetal mortality is very high, 70 per cent in this series.

Injury to the involved lower uterine segment is avoided by cesarean section, and this is the crucial point. Trauma, shock, uterine atony, and the inevitable postpartum hemorrhage are thereby circumvented. Timely blood transfusions and the more extensive use of cesarean section will lead to a notable reduction in the maternal and fetal mortality.

It is submitted that given a patient with placenta previa and a viable child, abdominal cesarean section gives the best results and calls for the least display of obstetric virtuosity.

40 EAST SIXTY-FIRST STREET

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#### OVARIAN PREGNANCY

WILLIAM C. THRO, M.D., NEW YORK, N. Y.

(From the Cornell University Medical College)

IN NONE of the cases of ovarian pregnancy reported has the gestation sac been completely surrounded by a corpus luteum, although lutein cells have often been found in the wall of an ovarian hematoma and might be considered as strong circumstantial evidence that the pregnancy had developed in a graafian follicle. In this instance the chorionic villi, as in practically every case reported were found lying free in a blood clot. The whole paraffin imbedding block was sectioned in an attempt to locate the embryo but the search was unsuccessful. It is generally concluded that the pregnancy is of short duration and the early death of the embryo is due to hemorrhage with a rapid degeneration of the embryo. The embryo may be



lost in the early rupture of the gestation sac. According to Hunter<sup>4</sup> an embryo was not found in 24 of the 43 cases reviewed by him.

Mrs. M. Y., No. 532, housewife, aged thirty-six years. Chief complaints were vaginal bleeding and pain in the lower left quadrant of the abdomen. Her past history was negative and there was no history of tuberculosis, cancer, or hemophilia.

The patient began menstruating at thirteen, duration of periods six days. She has had four children, all living and well; all the deliveries were normal, forceps not being used on any. She has never had any miscarriages.

For the last two months, preceding the operation, the patient complained of sharp pains in the lower left quadrant, these pains coming on only when the patient sat down or when she went to stool. Vaginal examination revealed a soft mass in the left side.

At operation, a left salpingo-oophorectomy was performed. At the operation, blood clots were found in the left side of the abdomen and in the culdesac. The



Fig. 1.—*c.l.*, corpus luteum; *c.v.*, chorionic villi.

left tube was enlarged and there was a blood clot at the fimbriated end. The left tube, together with the left ovary, were removed. The right tube and ovary were examined and found absolutely normal.

*Pathologic Findings.*—Adjacent to the fallopian tube, there was a mass 3 by 5 cm. in size. Cross-section of this mass showed a thin capsule enclosing a bluish purple mass like clotted blood and through which there were small grayish areas. The greater portion of the piece of tissue sectioned consisted of a large hemorrhage surrounded by a wavy layer of corpus luteum cells. Most of the chorionic villi seemed to be outside of the ring of corpus luteum cells but in one section there were chorionic villi near the hemorrhage and inside of the narrow ring of corpus luteum cells. For the most part, the chorionic villi were in patches and surrounded by red blood cells. In one section, there was a small graafian follicle. In all the sections the superficial syncytial layer, the subjacent epithelial layer of Langhans, and the vascular mucoid connective tissue center of the chorionic villi were demonstrable.

I wish to thank Dr. Herman Lorber of St. Mark's Hospital, New York, for permission to publish this case.

# Society Transactions

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## CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF JUNE 22, 1934

The following paper was presented:

Maternal, Fetal, and Neonatal Morbidity and Mortality. Dr. Fred L. Adair.  
(For original article see page 384.)

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Dippel, A. L.: Death of Fetus in Utero, Bull. Johns Hopkins Hosp. 54: 24, 1934.

The incidence of fetal death in utero during the last trimester of pregnancy in series of 25,000 consecutive deliveries was 1.2 per cent. The incidence is higher in the colored than in the white race with a ratio of 2.6 to 1. With multiparity the incidence increases. The majority of intrauterine deaths occur some weeks before the estimated date of confinement. Patients with acute toxemia of pregnancy usually fall into labor soon after death of the fetus, while the duration of retention in other cases is usually longer. More male than female fetuses die in utero.

Signs and symptoms of fetal death usually are clear-cut, and consist of failure of the mother to feel movements, absence of fetal heart sounds and of normal fetal body tone, boggy fetal head, crepitation of skull bones, and retrogressive changes in the size of the uterus. Further suggestive symptoms often occur and include maternal nausea, malaise, headaches, foul breath, bad taste in the mouth, a pronounced uterine souffle, a fall in basal metabolic rate, and retrogressive changes in the breasts. Helpful adjuncts to diagnosis, but not altogether reliable, are found in the Aschheim-Zondek test and in roentgenograms. Acetonuria is not a constant finding.

The causes of intrauterine death in order of their frequency are: syphilis; toxemia; loops of cord about some fetal part; intercurrent maternal disease; acts of violence to the abdomen; induction of labor; hemorrhage; fetal anomalies; true knots in and torsion of the umbilical cord; unusual shortness of cord; localized constriction of the cord; incarceration of the uterus; and uterine anomalies.

The gross maternal mortality in the series was  $\frac{1}{8}$  of 1 per cent and the corrected mortality  $\frac{1}{16}$  of 1 per cent. The morbidity rate was 23.25 per cent as contrasted with 17.75 per cent for the general clinic population. It is seldom necessary to induce labor.

The character of the labor pains was not significantly different from those of the patient with a living fetus.

C. O. MALAND.

# American Journal of Obstetrics and Gynecology

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EDITORS: GEORGE W. KOSMAK, M.D., AND HUGO EHRENFEST, M.D.

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## Editorial Comment

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### Birth Control and Limitation of Population

THE term "Birth Control" undeniably is a misnomer, but by common usage has been accepted as meaning the limitation and control of conceptions and not of births. The thought of limiting population is rationalized, in the main, by two ideas. According to the one, limitation of offspring benefits the community, the state, or the race; according to the other, it accrues to the benefit of an individual—the mother—or of a family. The claim has been made that mass limitation of births was necessary because human reproduction advanced by geometrical, but the means of livelihood only by arithmetical, progression. This fact would result ultimately in actual overpopulation in relation to the means of sustenance.

It long was believed that excess population was retarded and prevented, and the desirable equilibrium maintained by the large loss of life through war, pestilence, and famine. With the deliberate reduction of these potent forces of destruction, population inevitably would be increasing. As a matter of fact, war as a means of direct destruction of human lives has persisted in its previous significance. Famine, largely the result of war and closely correlated distress, at least in certain parts of the world, continues as a destructive agent, especially of children. Pestilence alone has almost been eliminated.

All these three factors together tend to reduce population, but with characteristic difference in their respective actions. War itself destroys the healthiest and strongest members of society; pestilence and famine, on the other hand, more likely will eliminate those least able to withstand hardship. The difference between selective destruction by war, and mere mass elimination, more typical for famine and epidemic disease, is of importance.

Widespread information and practice of contraception will lead to mass prevention of conception. However, even here we can recognize

an element of selective prevention. The intelligent, more responsible and economically favored groups of society have a better knowledge of the important details of contraceptive technic and are more desirous and able to apply it. At present a general effort is being made to encourage groups lower in the economic scale to make wider use of contraception. It should be clearly understood, however, that while these lower groups are struggling for existence, under present conditions often in vain, they by no means represent the less or least desirable strata of modern society.

Selective limitation, furthermore, demands proper consideration of the biologic basis underlying the entire problem of eugenic control. As yet, we know comparatively little concerning the effect of eugenic principles on human life. There is much evidence pointing to the conclusion that the offspring of certain types of defective individuals carry with them inheritable characteristics which perpetuate these defective qualities in the human race, and may be highly undesirable in their effect upon the individual and society.

One might say that there are two major aims in any program for the limitation or control of reproduction. One objective would be the selective limitation, with the thought of eliminating gradually the more unfit elements and stimulating the production of the more desirable individuals in our social organization.

Progressive epochs in the development of the human race have been surrounded with varying conditions of life. These have modified the type of individual who is best fitted to survive in the environment of that particular epoch. Physical development and adaptability were more important to survival in primitive life than any intellectual or moral attributes. The weak perished and the strong survived under such conditions. There were deliberate attempts among some nations and peoples to destroy the weaklings who were regarded as a burden upon communal or family life. Gradually, the intelligence of individuals became more and more important, which induced man to depend on various devices discovered and created through the exercise of his intellectual powers. These discoveries and inventions gave man definite superiority over other forms of animal life and also gave certain races and nations superiority over others. They also provided for the survival of many who would have perished under less favorable influences.

Religious and humanitarian influences then came into play and led to a much higher valuation of human life. The assembling of large numbers of people in cities favored the development of pestilence and disease. These were rampant during the Middle Ages and resulted in marked reduction of population, but were gradually overcome, as already has been pointed out, by medical measures and improvements in sanitation.

Malthus enunciated his doctrine relative to the principles of population over one hundred and twenty-five years ago. He advocated discouragement of early and improvident marriages and the cultivation of self-restraint. Statistics would seem to indicate that certain sections of the world are overpopulated at the present day. As a matter of fact, effective reduction of mortality from various causes has produced a corresponding increase in the percentage of survivals, or, in other words, resulted in an increase of longevity. Concomitant with this reduction in mortality for the last half century, there has been a steady decline in the birth rate (as well as in the actual number of births) among a gradually increasing number of the more highly civilized nations. The birth rate in many of these nations already has reached a point where one could expect a practical equilibrium in the population. Probably no one, however, is in a position to state the ideal relationship between birth and death rates, either for a nation or for the entire world.

The most significant rôle in the limitation of offspring today presumably is played by the use of contraceptive measures. These methods are by no means new, and in some form have been applied since earliest recorded times. The underlying principles are relatively simple. Primarily, they depend upon the prevention of fertilization by interference with the union of ovum and spermatozoid. This may be accomplished by mechanical means, such as an occlusive pessary or condom; by interruption or occlusion of the ducts conveying these cells, such as the fallopian tubes or the vas deferens; by chemicals which destroy the germ cells; by a physiologic method which depends on the time relationship between ovulation and insemination; and, finally, by permanent elimination of productive faculty through sterilization or castration.

The other method of prevention of offspring, i.e., actually of birth, consists in the willful termination of pregnancy. The latter, not generally used among modern civilized people, constitutes feticide or infanticide, and not so rarely results in matricide.

Thus, such methods easily fall into two general groups: (1) The prevention of life, assuming that life begins with fertilization, and (2) the destruction of life. Deliberate termination of pregnancy involves either the destruction of the fetus or embryo before it has reached a state of development consistent with extrauterine life, or destruction subsequent to the attainment of viability.

Our profession today is confronted with problems of a limited propagation which involve important medical, as well as sociologic, aspects. The basic principles of the various methods are essentially medical, so far as the determination of their respective value and proper application are concerned. The physician faces two problems—the welfare of the individual and the welfare of society, both affected by the

wider use of such protective procedures. The dominant ethical principles of the medical profession are the cure and prevention of disease, the mitigation of all suffering, and the saving and prolongation of life. Its ethical attitude, therefore, of necessity is definitely antagonistic to any procedure which involves the destruction of life at any point of its existence. Any procedure implying such destruction can be adopted by the physician only if the destruction of the potential life of the fetus, in his belief, will prolong or save the life of the mother. There is a tendency among some nations to regard destruction of the fetus as fully justified if this be the desire of one or both parents, or for sociologic reasons. It is difficult for physicians to accept such unrestricted ideas and, indeed, they are averse to many religious doctrines and legislative enactments dealing with the matter involved.

Only a plan of prevention based on interference with fertilization by some of the methods above mentioned will appeal to the great majority of civilized peoples. A method, to be acceptable, must be harmless, efficacious, not too unesthetic, and must be quickly, easily, and generally applicable, even among individuals of low intelligence. The success of any contraceptive measure depends upon the cooperation of individuals sufficiently intelligent to employ the method properly.

There are two essentially different aspects to the question of contraception: First, the method may be used voluntarily by the individuals concerned; second, the method may be enforced on individuals for the purpose of controlling or preventing reproduction, if for social, medical, or eugenic reasons it is undesirable to perpetuate a certain type or species. Enforced prevention of offspring might be justified or desirable (1) for a group with definite hereditary stigmas which, in all probability, would be transmitted to the offspring and make them undesirable elements in our social organizations; (2) for a group with questionable hereditary stigmas, but who, in themselves, are a menace to society and thus subject their offspring to environments which would tend to develop them into the same type of extremely unsocial elements. However, for this last group there admittedly would exist another and probably preferable method of protection, namely, prompt separation of such children from their parents both in their own interests and that of society.

It is a debatable question how far economic considerations per se should enter into the problem of limitation of offspring. There would seem to be available another means of solving this problem—the establishment of an economic system which would eliminate poverty sufficiently to permit the proper rearing of offspring of those citizens who do not constitute hereditary or socially undesirable elements in our civilization.

There is little evidence that first-, second-, and third-born children are superior to those later in the order of birth. The lives of many

illustrious leaders seem to point to the contrary. We should strive to encourage propagation among desirable human groups and discourage it among the undesirables. Probably no concrete plan can be developed at the present time for attaining these goals, but these objectives should be among our thoughts, and the necessary plans for their gradual attainment should be laid.

We must solve these questions along certain general lines. It might seem almost axiomatic that no procedures should be adopted or utilized which are harmful to individuals or to society. We must decide for each individual case whether contraceptive advice, instruction and devices are to be furnished upon eugenic, medical or sociologic indications, or whether such means should be dispensed for no other reason than the mere request of the individuals immediately concerned. It is generally conceded that temporary or permanent sterilization, therapeutic abortion and similar procedures should have clear-cut and definite indications for their employment.

In all of this agitation, it is necessary to distinguish between individual rights and collective obligations. On the one hand, the privilege of the individual to do and conduct himself as he desires is granted. He may eat, drink, smoke and behave harmfully to himself and even to others as long as he wishes until he is checked by regulation for the protection of others or even himself. On the other hand, there is no obligation on other individuals or groups to furnish information or supplies which might accord with personal desires or wishes, especially if they are not for the best interest of the individual or of society.

It is, therefore, essential for the physician that he determine what is best for certain individuals and for society, and then attempt to proceed in accord with definite eugenic, medical and sociologic indications to the best of our present knowledge, thus leading to human betterment. Our acts as medical men and as public servants must be consistent with the best individual and collective interest. Sociologists should proceed along the same lines and establish and announce reasons, if such exist, for giving contraceptive instruction to individuals.

A policy of selective limitation of births by voluntary and compulsory methods controlled by recognized public servants and agencies is not unreasonable. Granting the right to manage individual behavior, there is no public obligation to abet an individual in the free exercise of his acts. There is a clear distinction between an individual right to obtain, and a public obligation to supply, information and instruction. Last, but not least, any mercenary motive in considering and solving these problems certainly should be vigorously eliminated.

—F. L. A.

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Ectopic Pregnancy

Kriwsky, L. A.: The Extrauterine Pregnancies in the Njecajew Hospital in Leningrad, *Monatschr. f. Geburtsh. u. Gynäk.* 93: 292, 1933.

During five years (1927 to 1932) 168 cases of ectopic pregnancy were operated upon which with the previous 835 (between 1910 and 1926) make a total of 1,003 cases. In 56.6 per cent of the present series there was an external capsular rupture, in 35 per cent an internal capsular rupture, and in 8 per cent this point could not be determined with certainty.

A diagnostic pelvic puncture was rarely performed. In the treatment it was customary to be conservative. Usually only the involved tube was removed. Many of these women subsequently had normal intrauterine pregnancies whereas only five women (3 per cent) had a repetition of a tubal pregnancy. There were 4 deaths in the series of 168 cases, a mortality of 2.4 per cent. Three patients died of peritonitis and the fourth died from the anesthetic.

J. P. GREENHILL.

Siegel, P. W.: Etiology of Ectopic Pregnancy, *Zentralbl. f. Gynäk.* 57: 686, 1933.

The author is so impressed with the etiologic relation of previous operations, especially uterine suspension, to tubal pregnancy, that he states, "In a doubtful diagnosis of tubal pregnancy, special attention should be paid to a previous operative correction of uterine position," and that in such cases, "the possibility of a tubal pregnancy is enhanced."

WILLIAM F. MENGERT.

Osiakina, A. J., and Schmatok, K. D.: The Decidual Reaction in the Tube in Intrauterine and Tubal Pregnancies, and Its Significance for the Etiology of the Latter, *Monatschr. f. Geburtsh. u. Gynäk.* 94: 329, 1933.

The studies of the authors revealed that there is ordinarily no decidual reaction in the tube in the presence of an intrauterine pregnancy. On the other hand, in cases of tubal pregnancy, a decidual reaction does occur frequently and its function appears to be a protective mechanism against the invasion of the chorionic villi at the site of implantation. The decidual reaction cannot be regarded as an etiologic factor in the causation of tubal pregnancies. In 21 per cent of the cases examined, the decidual reaction developed irrespective of the location of the implanted ovum. In 8 per cent of the last 21 cases, the authors considered the decidual reaction to be the cause of the tubal pregnancy. A decidual reaction can only occur in a tube



where there is not a highly differentiated mucosa and in cases where the tubal mucosa resembles that of the uterus in structure. A lack of differentiation in the tubal mucosa is most likely dependent upon unfavorable conditions of living such as strong physical work, hunger and infectious diseases during the prepuberty period.

J. P. GREENHILL.

Bernhard, Erich: The Increased Frequency of Tubal Pregnancy and Its Causes, *Ztschr f. Geburtsh. u. Gynäk.* 105: 46, 1933.

Statistics prove that there is an increase in the number of tubal pregnancies in Basel. Many etiologic factors contribute in this increase. Among these are an increased gonorrhea morbidity, greater frequency of abortions, wide use of contraceptives, especially of the intrauterine type and the Kafka cap, and numerous local inflammatory conditions following chronic appendicitis. Only slight significance is given to the much accused hypoplasia of the genitalia in the etiology of ectopic pregnancy.

GROVER LIESE.

Dawydow, G. L.: Curettement of the Uterus for the Purpose of Interrupting Pregnancy in the Presence of Undiagnosed Extrauterine Gestation, *Monatschr. f. Geburtsh. u. Gynäk.* 91: 447, 1932.

The early stages of an intact extrauterine pregnancy cannot be diagnosed. It is only when disturbances arise that the correct state of affairs may be recognized. When a curettement is performed early in pregnancy, great care must be exercised because an ectopic pregnancy may be present. Dawydow reports a case where the uterus was curetted in the presence of an extrauterine gestation. In this case, as in many reported in the literature, the patient suffered no harm. According to the author the external bleeding which occurs in cases of ectopic pregnancy is due either to the uterine endometrium or to the escape of blood from the gravid tube. A disturbed ectopic pregnancy may run the course of a tubal abortion or a tubal rupture, or a combination of these two, as occurred in this case.

J. P. GREENHILL.

Hatleberg, C. B.: Diagnosis and Treatment of Ectopic Pregnancy, *Wisconsin M. J.* 31: 530, 1932.

Ectopic pregnancy is difficult to recognize and yet it supplies the operating room with more emergencies than any other lower abdominal lesion except acute appendicitis. Irregular vaginal bleeding is probably the commonest diagnostic symptom, as 84 per cent of the cases show vaginal bleeding. Pain is the next most important symptom. In about 85 per cent of the cases a soft boggy mass is palpable on the affected side. The leucocyte count will average about 14,000. Colpotomy is very helpful in differential diagnosis and sometimes the ectopic pregnancy can be removed through the vaginal incision. Salpingitis is the condition most difficult to differentiate from ectopic pregnancy. Uterine abortion usually shows more profuse bleeding and a more definite history of amenorrhoea. The treatment is immediate operation, removing the affected tube and controlling hemorrhage. The author suggests that a considerable part of the first shock is due to rupture of an abdominal viscus, rather than to any large loss of blood. Ether acts as a stimulant in these cases if used for a short period and is the anaesthetic of choice. The average mortality is about 4 per cent.

J. THORNWELL WITHERSPOON.

Sserebroff, A. I.: Types of Operations for Tubal Pregnancy, Arch. f. Gynäk. 148: 364, 1932.

Sserebroff reviews the literature in regard to the incidence of tubal pregnancy following removal of the opposite tube for tubal pregnancy. He concludes that the incidence of the occurrence of a second tubal pregnancy in the remaining tube is 5 per cent. In the Leningrad clinic the incidence was 4 or 5 per cent. In addition, over 52 per cent of women were sterile following the occurrence of one tubal pregnancy and 14 per cent conceived but aborted. For these reasons the author is firmly convinced that both tubes should be removed whenever a patient is operated upon for tubal pregnancy.

RALPH A. REIS.

Saass, Carl: A Recurrence of Tubal Pregnancy in the Same Tube Following a Previous Ectopic Pregnancy With Partial Resection and Ligation, Zentralbl. f. Gynäk. 54: 2590, 1930.

Although ectopic pregnancy can occur in any part of a tube, the author could not find another case in the literature of recurrence of tubal pregnancy in one and the same tube. Five years before the present admission a thirty-five-year-old woman had had an ectopic pregnancy removed from the ampulla of the left tube by simple resection of the ampullic end of the tube. The stump was ligated. She returned, having had no pregnancies in the five-year interval (at the previous operation the right tube and ovary were normal) with symptoms exactly similar to those of her preceding ectopic. An ectopic pregnancy in the stump of the left tube was found and the tube was removed. Removal of the whole tube should be the operation of choice.

WILLIAM F. MENGERT.

Schroderus, M.: Four Cases of Unruptured Interstitial Tubal Pregnancy, Acta obst. et gynec. Scandinav. 14: 48, 1934.

According to statistics of the last few years the frequency of interstitial tubal pregnancy probably is less than 1 per cent among all tubal pregnancies. In interstitial as well as in other forms of tubal pregnancies it is possible and advisable to distinguish between tubal rupture and tubal abortion. One hundred and nine cases of interstitial tubal pregnancy have been reported since 1925. The author adds three cases of his own, and describes the clinical picture of interstitial abortion in the initial stage. He emphasizes that the syndrome is comparatively uniform and characteristic. The early diagnosis of interstitial tubal abortion does not seem to be difficult to make.

J. P. GREENHILL.

Hasselblatt, Robert: A Case of Primary Abdominal Pregnancy, Zentralbl. f. Gynäk. 56: 404, 1932.

A twenty-four-year-old woman who had had an abortion two and one-half years previously, and an intraligamentous cyst on the right removed by a right salpingo-oophorectomy one year previously, entered the clinic complaining of sudden abdominal pain and fainting. She was in collapse apparently from an intraabdominal hemorrhage. At laparotomy the uterus was found enlarged to the size of a four months' pregnancy, and the left tube and left ovary were seen completely free and normal. On the right side the old operative site was smooth and unaffected. A 28 cm. living fetus was removed but died after a few minutes. The placenta was attached to the right side of the uterus which was removed in order to assure hemostasis. Serial

sections of the right uterine cornu were made and no evidence of a right tube or of any connection between the ovum and the uterine cavity was found. The author believes that this case satisfies Veit's criteria for a primary abdominal pregnancy which are: (1) the fetus must be living, (2) must be in a living connection with its matrix, (3) the tubes and ovaries must be free and independent of the ovum. The author has collected 33 such cases from the literature.

WILLIAM F. MENGERT.

Apajalahti, A.: The Fate of Women Operated Upon for Tubal Pregnancies, *Acta obst. et gynec. Scandinav.* 12: 329, 1932.

The author attempted to follow up a series of 300 women who were operated for tubal pregnancies from 1920 to 1930 at the Women's Clinic in Helsinki. Among 138 women who had hematoceles and adhesions at the time of operation he found that the type of operation played a distinct rôle in the subsequent health of the individual. Thus among those in whom the Beuttner high method of peritonealization was employed 88 per cent were free from annoying symptoms; whereas only 44 per cent of those in whom this type of peritonealization was not employed had no complaints. Furthermore, postoperative intestinal obstruction occurred in 3 out of 94 patients before the Beuttner method of peritonealization was employed, but no cases occurred among the 116 cases where it was used.

Among the 79 women who were capable of conceiving, 41 did become pregnant, and had 29 full-term deliveries, 20 abortions and 3 extrauterine gestations. The author adds that 18 women had two ectopic pregnancies. On the basis of a four years' interval, the frequency of repeated ectopic pregnancy was 7.3 per cent of the total number but if based only upon those who subsequently became pregnant the incidence was 17 per cent.

J. P. GREENHILL.

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### Dr. Franklin H. Martin

Dr. Franklin H. Martin died in Phoenix, Arizona, March 7. An extended obituary will appear in the April issue of the Journal.

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*(Moffett Studio)*

**FRANKLIN H. MARTIN**  
1857-1935

# American Journal of Obstetrics and Gynecology

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## IN MEMORIAM

FRANKLIN H. MARTIN

1857-1935

FRANKLIN H. MARTIN, friend, dreamer, idealist, among the greatest in medicine, died quietly on March 7, 1935, in Phoenix, Arizona. Born in Ixonia, Wisconsin, on July 13, 1857, of pioneer stock, Franklin Martin remained, throughout his long and constructive life, a pioneer in medicine, a teacher and an organizer.

His education at the rural public schools in Wisconsin was haphazard, and often interrupted because of the adverse fortunes of his family, and Frank Martin, as a young boy, began devising ways to supplement the family income: weeding gardens, herding sheep, chopping wood, helping with the haying, making bricks, or whatever came to hand. The education he got he more than earned, and what he learned stuck with him, in spite of the many moves from place to place, from one crude school to another. In 1876, while working on a farm, he decided suddenly that, in spite of the obvious hardships this would entail, he would "be a Doctor," and so, the following fall, he attached himself to Dr. William C. Spalding in Watertown, Wisconsin, to read and study. There he met and formed a friendship with Frederick Parkhurst, who likewise was studying under a local physician, and these two young men, nothing daunted by their poverty, decided to enter the Chicago Medical College (now Northwestern University Medical School). So, in the fall of 1877, he embarked upon the rather hazardous, and certainly strenuous business of a medical course, and in 1880 Franklin Martin emerged with an M.D. degree. The year following his graduation he spent as an interne at the Mercy Hospital in Chicago.

From then on he became a teacher, educator and organizer, as well as entering private practice in the field of gynecology. His interests widened rapidly, and he published, from time to time, numerous papers

on gynecologic subjects. His tenacity in securing an education, and making a living while doing so, stood him in good stead as the years passed, as well as playing a large part in the winning of the charming Miss Hollister for his wife in 1886, in spite of the opposition of her parents. This same quality, as well as his perseverance, dynamic personality and tireless energy, aided him in drawing to him, and having cooperate with him, people who could and did serve him to the best of their ability. In 1888 he assisted in organizing the Post-Graduate Hospital School of Chicago.

The adage "The boy is father to the man," as Dr. George Crile points out in his foreword to *The Joy of Living*, seems especially apt in the case of Franklin Martin, for the boy, doggedly making bricks, soon matured into the man who laid many corner stones, and his first outstanding accomplishment was the establishment of *Surgery, Gynecology and Obstetrics* in 1905, to which, in 1913, was added the *International Abstracts of Surgery*. He edited this journal from the day of its inception to the time of his death. This first successful venture and its development led to the founding of the Clinical Congress of Surgeons of North America in 1910, and the founding of the American College of Surgeons in 1913. Later, in 1921, he founded and directed the Gorgas Memorial Institute of Tropical and Preventive Medicine.

As has often been pointed out, Franklin Martin's plans for the advancement of surgery could not have been so fruitful without the interest and cooperation of leaders in the field of surgery, but, here again, his power of attracting people and binding them to him, his vivid imagination, his fearlessness, his sincerity and faith, courage and determination, were all in his favor, and those who knew him well, and worked with him, trusted and believed in him. Probably no other man was more alive to the changing conditions in public institutions, more interested in political trends and social economics. He was ever on the alert for, and quick to recognize, trends which would be useful and practical for the improvement of the medical profession.

During the World War, in 1916, President Woodrow Wilson asked him to head the development of medical participation, and he became the Chairman of the General Medical Board of the Council of National Defense, and, again, it was he who was responsible for the development of the Volunteer Medical Service Corps. He served as a Colonel in the Medical Corps of the United States Army, and was with the American Expeditionary Forces for three months. He has left a valuable record of the work of the Medical Section of the Council of National Defense, published in book form in 1934.

The success of his leadership and organizational efforts brought him many honors and recognition from all over the world. He extended the influence of the American College of Surgeons to South American and European countries, and because of this work, he received the

honorary Fellowships and membership of many of them. He was given an LL.D. degree from Queen's University, Belfast, Ireland; from the University of Wales, Cardiff; from the University of Pittsburgh; the degree of D.Sc. from Northwestern University, and the degree of D.P.H. from Detroit College of Medicine and Surgery. He was decorated with the Companion Order of St. Michael and St. George by King George V of England in 1919, and received the Distinguished Service Medal of the United States Government, as well as the Order of Commander of the Crown of Italy.

His offices were too numerous to enumerate in detail, but, in addition to editing *Surgery, Gynecology and Obstetrics* for thirty years, he was active Director of the American College of Surgeons for twenty-two years. He was President of the American Gynecological Society; President of the American College of Surgeons in 1929; Trustee of Northwestern University from 1921 to 1931, and Chairman of the Board of the Gorgas Memorial Institute from 1921 to the time of his death. Dr. Martin accepted membership on the Advisory Editorial Board of this JOURNAL at the time of its founding and continued his interest in the publication up to the time of his death.

Franklin Martin also contributed several well-known articles and books to medical literature: "The Treatment of Fibroid Tumors of the Uterus"; "Treatise on Gynecology"; "South America From the Surgeon's Standpoint"; "Australia and New Zealand"; "The Joy of Living," an Autobiography, in two volumes, and "Digest of the Proceedings of the Council of National Defense During the World War."

Although Franklin Martin was a shy and reserved man, his various activities and contacts all over the world made him genial, cultured and well-informed. He was a man of distinguished appearance; one who dominated a group and stood out from it. His intelligence, kindness and charm made friends for him wherever he went, and there are eminent people from Australia to Hungary who will feel a great personal loss in the passing of Franklin Martin, who was as distinctly an individual as he was an organizer and leader of men.

C. Jeff Miller.



## Original Communications

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### RENAL FUNCTION IN THE TOXEMIAS OF PREGNANCY\*

WILLIAM J. DIECKMANN, B.S., M.D., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, The University of Chicago, and The Chicago Lying-in Hospital)*

APPROXIMATELY 8 per cent of the patients delivered in a maternity hospital have toxemia. This is characterized clinically by the occurrence of one or more of the following signs: Hypertension, albuminuria, or edema. In addition, there may be symptoms of various visual disturbances (diplopia, scotomas, amaurosis), dizziness, epigastric pain, vomiting, or oliguria. The classical case of toxemia of pregnancy occurs in primiparas in whom the onset of symptoms is manifested in the last trimester, particularly in the last two to six weeks of pregnancy. The disease is termed preeclampsia, but if the patient has convulsions and/or coma in addition to one or more of the signs, it is called eclampsia. Apparently the condition subsides rapidly after delivery or death of the fetus, and leaves the patient with a normal cardiovascular-renal system. However, toxemia may recur in subsequent pregnancies, but the symptoms and signs will appear, as a rule, earlier than in the first pregnancy.

The recurrence or persistence of toxemia has been variously designated as chronic, recurrent or latent nephritis, recurrent toxemia of pregnancy, or low reserve kidney if there is no apparent increase in severity. DeSnoo and Adair were among the first obstetricians to add essential hypertension to the list. When these symptoms appear during pregnancy it is of the utmost importance to know as soon as possible whether the patient is suffering from preeclampsia, which probably will not recur in subsequent pregnancies, or whether she has a chronic nephritis or an essential hypertension. Both of these diseases are progressive and their courses are usually accelerated by the pregnancy. We have never observed a case of acute or chronic nephritis in which the patient improved during pregnancy, but have seen patients with hypertension and/or albuminuria in whom there was no perceptible increase in the disease during pregnancy.

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\*Aided by a grant from the Josiah Macy, Jr., Foundation.

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

The incidence of the toxemias of pregnancy for the Cornell University Clinic is 15.6 per cent and for the Johns Hopkins Clinic 9.4 per cent, as reported by Stander; Washington University Clinic, 3.8 per cent, according to Schwarz and Wegner, and 6.7 per cent for the University of Chicago Clinic. A conservative estimate of the number of patients with toxemia of pregnancy in the United States each year would be 100,000. Thus some idea is given of the importance of the toxemias of pregnancy to both the individual and to the race.

Innumerable reports have been published in the past fifty years, some confirming and others denying that permanent renal damage occurs in patients with pre-eclampsia or eclampsia. Reports from various German clinics indicate that permanent renal damage from eclampsia or preeclampsia is unusual, if not actually rare. Schultz, in 1932, in a follow-up study of 780 toxemic patients from 1900 to 1930, was able to examine 124. He found 13, or 10.5 per cent, with hypertension and/or albuminuria. In the same clinic, in 1925, Nevermann studied 60 patients who had had eclampsia or preeclampsia in the preceding twenty-five years, and found 14, or 23.4 per cent, with hypertension or albuminuria. Seven years later when these same 14 patients were seen by Schultz, their condition had not been made worse. Therefore, he concludes that the renal affections of eclampsia always heal and that the evolution into chronic nephritis is exceptional. It is usually possible to discover some other cause for renal disease in the history of such a patient.

There is lack of agreement among the British authors, but the majority believe that a considerable proportion of the patients with eclampsia or preeclampsia have resultant permanent renal damage.

Stander, Peckham, and Harris, in this country, state that from 20 to 75 per cent of the toxemic patients have evidence of chronic nephritis when examined one year later. There is no doubt that the occurrence of toxemia predisposes to a recurrence in subsequent pregnancies. Young and Sym state that from 40 to 45 per cent of the patients with eclampsia have some evidence of toxemia in subsequent pregnancies. We have noted in a series of 438 toxemic patients that 90, or 20 per cent, gave histories of previous toxemia. In 29 patients with histories of convulsions in previous pregnancies, 26, or 90 per cent, had some evidence of toxemia during the pregnancy under our observation.

An explanation of these conflicting reports may be found in the criteria used in making a diagnosis of nephritis. For the past twenty-five years a diagnosis of chronic nephritis was made by the obstetrician on the basis of the presence of hypertension, albuminuria, and/or edema if one or more of these signs (1) persisted for more than three weeks postpartum; (2) appeared in the first half of pregnancy, especially in multiparas; (3) recurred in subsequent pregnancies, or (4) if a history of nephritis or hypertension was obtained from the patient.

Such a classification was satisfactory for a time, but with knowledge gained by observations made on men, nonpregnant women, by various renal functional tests and postmortem examinations, it soon became evident that the diagnosis of chronic nephritis was not suitable in many cases. In some of them the only abnormal finding would be a hypertension, and the cause of death would be due to a hemorrhage, usually cerebral, rather than renal failure. These patients would be classified as having a primary or essential hypertension. In the other

group of patients who gave a history of acute glomerulonephritis with a possible exacerbation during pregnancy, or an acute toxemia of pregnancy of long duration, producing renal changes similar to those found after an acute nephritis, the classification would be chronic glomerulonephritis. The correct diagnosis is of importance to the physician because by clarifying the clinical and pathologic condition he is a step closer to the etiology, prevention, and cure. Furthermore, he will know better how to manage the pregnancy, the complications to be anticipated and how to prevent them, and whether or not the present pregnancy should be interrupted and future pregnancies prevented.

The internist requires a history of a typical acute attack of nephritis or symptoms and signs of kidney pathology, as well as evidence of renal impairment, before he will make a diagnosis of chronic glomerulonephritis. The German authors insist upon similar evidence but very few, if any, of the English or American obstetricians make this distinction. Undoubtedly, many of the toxemic patients who are classed as having chronic nephritis have hypertension as the principal sign, which may be caused or aggravated by the pregnancy. The blood pressure may either return to normal between pregnancies or remain permanently elevated, the latter occurring usually after repeated pregnancies. At the Johns Hopkins Clinic (Harris, Stander, Peckham) hypertension in pregnancy has never been recognized as a disease entity. While many of the patients with hypertension will ultimately have kidney damage, as proved by renal function tests and autopsy, the pathologist is unable, in some cases, to state whether the glomerulus was destroyed as a result of glomerulonephritis or nephrosclerosis. We believe, according to the data at hand, that an *increase in blood pressure* is usually the first, and ordinarily the most frequently encountered, sign of the recurrent toxemias of pregnancy.

Obstetricians long have spoken of the load produced by pregnancy on the cardiovascular-renal system, but never have been able to define just what it is. It certainly is not the metabolic waste products of the fetus since it manifests itself when the fetus is still small, in many instances only 8 or 10 cm. in length. We believe that the load is caused by the marked changes in the maternal metabolism produced by the pregnancy. Some of these changes are: (1) A tendency toward a positive water balance (edema); (2) a decrease in serum protein; (3) an alteration in the nitrogen, fat, carbohydrate, and mineral metabolism; (4) the congestion of many tissues and organs; (5) the increased permeability of vessel and cell walls; (6) the increased absorption of toxic substances from the intestines, and decreased elimination of waste products due to constipation, and (7) increased irritability of the central nervous system, etc.

These marked alterations in metabolism and physicochemical changes in the cell wall may place an additional strain on the vascular system and kidneys. However, the load imposed by pregnancy is demonstrated best, perhaps, by noting the rapid abatement of symptoms and signs in cardiac, nephritic, or toxemic patients subsequent to the termination of pregnancy at two to five months, long before there could be any mechanical factor because of the size of the fetus.

We have divided the patients into convulsive and nonconvulsive toxemia, the latter comprising the acute and chronic types. The patients with nonconvulsive toxemia have been divided as follows: Group I (acute or preeclamptic toxemia) consists of patients of whom the majority are primiparas, who have had normal pregnancies until the last trimester, when the symptoms and signs of toxemia developed. Group II comprises those patients who gave histories of previous toxemia of pregnancy, acute nephritis (rare), or hypertension. Group III includes multiparas in whom the past history has been negative. In another group we have listed the patients who had had abruptio placentae because of the reported frequency of chronic nephritis (recurrent toxemia) as a cause or the result of abruptio placentae, and the high incidence of cortical necrosis of the kidney reported in association with it.

#### METHOD

The patients were admitted to the hospital and kept in bed. An enema or mild cathartic was given, and after at least twenty-four hours (usually 48 or more) the renal function tests were performed. Food and fluids were stopped the night preceding the test at 6:00 P.M. The patient's bladder was emptied at 6:00 A.M. A catheter was inserted at 9:00 A.M. and left in place for two hours, specimens being taken at 9:00, 10:00, and 11:00 A.M. At 9:00 A.M. the patient was given a breakfast which consisted of fruit, toast, cereal, and 200 c.c. of water. No coffee, tea, or milk was given. The urine specimens were taken to the laboratory immediately, measured, and 10 c.c. of the 9:00 A.M. specimen were centrifuged at 1,200 r.p.m. for ten minutes. The volume of sediment was noted and 9.5 c.c. were discarded. The remainder was shaken up and a portion transferred either to a blood or a mold counting chamber, and the average number of formed elements per low power field was counted. The specific gravity was determined on all three specimens, either by the gravimetric method, using 10 or 25 c.c. amounts, or by a certified pycnometer. Blood was obtained at 10:00 A.M. and a Folin-Wu filtrate was made. Urea in both blood and urine was determined in the majority of cases by Leiboff's acid hydrolysis method. The nonprotein nitrogen and many other constituents were determined on all blood specimens. All urine specimens were tested for albumin by heat and acetic or sulphosalicylic acid. Ambulatory cases were catheterized only once to obtain a specimen suitable for microscopic examination and albumin determination. All of the microscopic examinations have been made by the author.

#### RESULTS

From 1925 to March 31, 1934, approximately 850 patients with moderate and severe nonconvulsive toxemia, and 82 with eclampsia have been studied. Various blood and urine examinations, renal function tests, and many other special examina-

tions have been made in these toxemic patients in an endeavor to determine (1) the severity of the condition, (2) some criteria for a prognostic guide, and (3) some means of classification. The various renal functional tests used have been the concentration: diuresis, phenolsulphonephthalein, MacLean's urea concentration, urea clearance, and creatinine filtration. A short summary of our findings with these various functional tests, and a complete report of the results with the urea clearance will be given. These data will demonstrate that in both normal and toxemic pregnancy there is some decrease (at times marked) in the figures for many of the renal functional tests, probably due to extrarenal rather than renal causes, because soon after delivery many of the various functional tests show marked increases.

In Table I we have given the number of patients, age, and parity for the various groups. All of the patients had very definite evidence of toxemia, and approximately 80 per cent are classified as having a moderate or severe toxemia, according to the criteria used by us. The increasing age and multiparity are of interest in Groups II and III, as compared with Group I. These figures would seem to indicate that the incidence of toxemia increased with the age and parity of the patient. In Group I, the age and multiparity of several patients are at variance with the usual case of preeclampsia, but the histories, course and changes in blood volume, as described by us previously, were typical for acute toxemia.

TABLE I

	NONCONVULSIVE TOXEMIA			ECLAMPSIA	ABRUPTIO PLACENTAE
	GROUP I PRE- ECLAMPSIA	II HISTORY OF TOXEMIA	III NO HISTORY OF TOXEMIA		
<i>Age:</i>					
Minimum	18	19	24	16	24
Maximum	40	43	46	40	42
Average	26.4	31.9	34.3	25.9	33
<i>Parity:</i>					
Minimum	1	1	1	1	1
Maximum	8	15	13	9	14
Average	1.73	4.1	5.4	1.9	7
<i>Primiparas:</i>					
Number of cases	35	4		20*	7*
Total cases	46	58	38	26	24

\*Eclampsia occurred in the first pregnancy in 20 patients, and abruptio placentae in 7.

The concentration-diuresis test is the simplest, and if the results are within normal limits, it is of great value; if the results are borderline or below normal it is almost useless. Normal pregnancy causes certain metabolic and physicochemical changes in the body which alter the excretion of water and solids by the kidney and thus affect renal functional tests.

Slemons, in 1904, noted in three normal pregnant patients that the average twenty-four-hour urine comprised 72, 53, and 48 per cent of the fluid taken by mouth, but that after delivery the urine volume increased to 81, 63, and 69 per cent, respectively, which he stated were essentially the average figures for men. In one patient with a dead fetus in utero the urine was 93 per cent before delivery and 85 per cent after delivery.

Holtermann, basing his opinion on the Kaufmann edema test,<sup>1</sup> stated that 25

<sup>1</sup>One hundred and fifty cubic centimeters of water every hour from 7:00 A.M. to 1:00 P.M., and a comparison of the 8, 9, 10, and 11 A.M. specimens with those at 12 and 1, with the foot of the bed raised 25 cm. at 11 A.M.

per cent of all pregnant women without manifest edema showed latent edema. He did not regard this method as a test of heart function in pregnancy, but as a test of the capillary circulation, since he considered the edema of pregnancy to be due to increased permeability of the capillary walls.

Janney and Walker, using a water elimination test,<sup>2</sup> noted that in normal pregnancy the ability of the kidneys to excrete water steadily decreased, reaching a minimum of 67 per cent at thirty-six weeks. After delivery the urine volume steadily increased and by the ninth postpartum week it formed 92 per cent of the intake, without correction for the breast milk. In six toxemic patients the average output of urine was 17 per cent of the normal. In a subsequent report they demonstrated that the kidneys were far more efficient with the patient in the horizontal than in the vertical position, thus indicating the value of absolute bed rest not only in the toxemias of pregnancy, but in all patients with seriously impaired renal function.

We have repeated their work, and in a small series of 12 normal patients at term the percentage of urine was 36 per cent before and 78 per cent after delivery. Thus it is evident that there is a disturbance in the water excretion during pregnancy, and that any test which involves either the measurement of the volume of urine or the determination of the excretion of some substances for a given period will be decreased.

In Tables II, A and II, B are listed the means for the three-hour and one-hour volumes of urine (average of two one-hour periods) in normal and toxemic patients. The toxemic patients before delivery show this decreased water elimination or oliguria better than the normal patients who had not fasted for fifteen hours. Many patients did not secrete any urine between 9:00 A.M. and 10:00 A.M., and even at the end of the second period there would be only 10 or 20 c.c. These same patients after delivery, under identical conditions, would excrete 40 to 80 c.c. or more per hour, despite the extra need of water for lactation. In Table II, A, the difference before and after delivery in pre-eclampsia is of significance and emphasizes the oliguria which is characteristic of this disease. In Table II, B, the difference before and after delivery in Group III is of significance. In this group we thought that because of no previous history of toxemia the figures for the renal functional tests would be higher than in Group II. However, these patients had lower figures, indicating that the condition was either a different one or that the history was incorrect. They demonstrated the insidious onset of vascular-renal disease.

In Table II, C are listed the means for the specific gravity of the urine. While the difference between the antepartum and postpartum means in Groups I, II, and III is not significant, the data for each mean are obtained from the same patients; therefore, we believe that our figures do show the direction of change. The frequency of distribution, likewise, shows a preponderance of higher specific gravity

<sup>2</sup>All-night fast, intake of 200 c.c. of water every thirty minutes from 9:00 A.M. to 11:30 A.M., and a comparison of the volume of urine from 9:30 A.M. to 1:00 P.M., with the total intake of 1,200 c.c.

TABLE II

	NONCONVULSIVE TOXEMIA											ECLAMP- SIA	ABRUPTIO PLACENTAE	
	NORMAL PREGNANCY		GROUP I		II				III					
			PREECLAMPSIA		HISTORY OF TOX- EMIA		NO HISTORY OF TOXEMIA							
	A.P.	P.P.	A.P.	P.P.	A.P.	P.P.	A.P.	P.P.	A.P.	P.P.	P.P.	P.P.		
<i>A. Volume of Three-Hour Urine in Cubic Centimeters</i>														
Total cases	18		14	25	35	25	17	12	26	25				
Mean	70.8		50.0*	115.5*	108.9	101.5	93.4	81.3	118.3	110.5				
Standard deviation	57.8		25.9	54.5	55.2	62.2	37.4	38.8	67.6	52.5				
Probable error	9.20		4.67	7.35	6.30	9.34	6.11	7.56	8.95	7.08				
<i>B. Volume of One-Hour Urine in Cubic Centimeters</i>														
Total cases	27	10	22	27	37	31	24	20	26	26				
Mean	55.1	47.5	36.4	54.2	45.6	66.5	38.5*	73.8*	65.3	73.1				
Standard deviation	46.9	31.7	23.2	40.3	37.7	62.1	24.5	57.9	54.0	53.0				
Probable error	6.09	6.75	3.34	5.23	4.18	7.50	3.37	8.73	7.15	7.01				
<i>C. Specific Gravity of Three-Hour Urine</i>														
Total cases	29	25	14	22	34	32	17	10	23	27				
Mean	1.022	1.029	1.016	1.019	1.019	1.020	1.018	1.019	1.016	1.018				
Standard deviation	0.0069	0.0071	0.0054	0.0076	0.0063	0.0074	0.0050	0.0057	0.0098	0.0079				
Probable error	0.0011	0.0012	0.0011	0.0012	0.0008	0.0011	0.0008	0.0012	0.0014	0.0010				

Means, standard deviations, and probable errors were derived from the usual frequency tables.

\*Significant difference.

A. P. = Antepartum.

P. P. = Postpartum.

after delivery. The normal pregnant woman is able to excrete urine with an average specific gravity of only 1.022 after a fifteen-hour fast, probably because of the excess amount of water in her tissues (physiologic edema). With longer fast periods or after delivery or death of the fetus she is able to excrete urine with a specific gravity of 1.030 or even higher. The relatively low specific gravity in pregnancy is due to a decreased amount of solids, especially urea and chlorides. Data on urea are given in Table III, C, but since the specific gravity varies more with changes in electrolytes, any decrease in their concentration will lower the specific gravity. Normally, the kidney can concentrate NaCl to 1.3 per cent, but in many analyses in pregnancy we have seen only a few patients who could concentrate it to this degree. The range is from 0.01 to 0.9 per cent, with an average of 0.5 per cent. Large amounts of ingested chloride are excreted by an increase in the volume of urine. This low concentration of chloride in the urine, we believe, is due to changes caused by pregnancy in the permeability of the vessel and cell walls, which permit water and chloride to escape from the vascular system into the cell and interstitial spaces, but retard the return. The rapid disappearance of intradermal wheals of physiologic saline solution in pregnancy adds additional support to the opinion that the change is in the tissues and not in the kidneys.

The specimens of urine obtained on admission from 26 patients with eclampsia were always concentrated and highly colored, but contained an average concentration of NaCl of only 0.185 per cent (range 0.006 to 0.0550). In 12 patients with preeclampsia the average concentration of NaCl was 0.169 per cent (range 0.015 to 0.560). The urea nitrogen was also usually less than 500 mg. per cent. This low concentration of NaCl is probably extrarenal in origin because within a few hours the excretion of NaCl may be normal. In one patient with eclampsia three specimens of urine within the first twelve hours, with volumes of 12, 40, and 720 c.c., had a concentration of 0.21, 0.77, and 0.88 per cent, respectively. Thus if the specific gravity of the urine in pregnancy is 1.022 or more, there is no evidence of renal impairment, but if it is less, the determination is of comparatively little value.

The phenolsulphonephthalein test was used in some 60 cases of severe toxemia. Only five patients with marked renal impairment excreted less than 50 per cent. Of course, in the eclamptic or preeclamptic patients with oliguria or anuria the excretion of the dye is diminished, but these same patients will have an excretion of 80 to 90 per cent of the dye as soon as the urine volume is normal, which has occurred in many cases both before and after delivery within twelve to twenty-four hours of the acute suppression of urine.

The MacLean urea concentration test was discarded because the comparatively low values of urine urea in both normal pregnant and



TABLE III

	NONCONVULSIVE TOXEMIA												ABRUPTIO PLACENTAE
	NORMAL PREGNANCY		GROUP I PRE- ECLAMPSIA		II HISTORY OF TOXEMIA		III NO HISTORY OF TOXEMIA		ECLAMPSIA		P.P.		
			A.P.	P.P.	A.P.	P.P.	A.P.	P.P.					
<i>A. Blood Nonprotein Nitrogen in Milligram Per Cent</i>													
Total cases	14		27	27	39	28		23	20		30	21	
Mean	23.8		28.2	31.7	27.9	30.5		29.5	31.2		29.3	32.1	
Standard deviation	4.82		5.3	4.8	6.4	6.8		6.2	6.4		5.1	6.4	
Probable error	0.069		0.69	0.66	0.69	0.87		0.87	0.97		0.83	1.15	
<i>B. Blood Urea Nitrogen in Milligram Per Cent</i>													
Total cases	28	10	26	30	39	33		24	23		26	26	
Mean	12.18	14.0	13.7	16.2	14.4	16.1		15.4	16.4		14.7	15.3	
Standard deviation	3.67	3.87	3.4	3.5	4.2	4.4		5.4	4.6		5.0	3.7	
Probable error	0.468	0.725	0.45	0.45	0.45	0.52		0.74	0.65		0.80	0.59	
<i>C. Urine Urea Nitrogen in Milligram Per Cent</i>													
Mean	778.0	1001.0	479.0	632.0	588.0	654.0		452.0	700.0		508.0	540.0	

Means, standard deviations, and probable errors were derived from the usual frequency tables.

Means, standard deviations, and probable errors were derived from the usual frequency tables.

toxemic patients, even after urea by mouth, made the test of little value for diagnosis or prognosis.

The Addis technic for the microscopic examination of the urine was used in all cases, but was modified.\* The Addis count is of the utmost importance in toxemic patients, but it is time-consuming if carried out according to the original technic, and we, therefore, suggest the modification.

In a previous publication we have given our results for the blood nonprotein nitrogen in the toxemias of pregnancy, but believe that the comparison of urea nitrogen and nonprotein nitrogen on the same patient is of importance. Therefore, in Tables III, A and III, B are listed the means for blood nonprotein nitrogen and urea nitrogen for the series reported in this paper. The difference between the means for the nonprotein nitrogen and the blood urea nitrogen before and after delivery was of no significance in all of the groups, but it should be noted that the means were always higher after delivery. Patients with a nonprotein nitrogen of 55 mg. per cent or blood urea nitrogen of 30 mg. per cent or more are not included in the statistical tables. These patients (relatively rare) are not representative of the vast majority of toxemic patients, and the inclusion of data from such cases would not give a proper conception of the toxemias of pregnancy. Thus in 2,252 analyses of the blood on approximately 600 toxemic patients, the nonprotein nitrogen was more than 50 mg. per cent in 21. In 342 blood urea determinations on 190 toxemic patients there were only 13 with more than 30 mg. per cent. As a rule, patients with renal impairment of sufficient severity to cause nitrogen retention do not conceive.

Since the introduction of the manometric determination of urea by Van Slyke, many extremely low figures for urea nitrogen have been reported. We have analyzed various standard solutions of urea and blood with Van Slyke's manometric, Leiboff's acid hydrolysis, and the xanthidrol methods, and if done carefully, with special emphasis on the proper clearing of the manometer (possible poisoning of the urease by the mercury salts), consistent results have been obtained. However, in the routine determination of blood urea in pregnancy by the manometric method in our laboratory and in two others, the figures in the majority of cases have been lower than those obtained by other methods. In a fair proportion of the cases the manometric data are undoubtedly incorrect. Thus Hurwitz and Ohler, in reporting their series of urea clearances in the toxemias of pregnancy, state that the average nonprotein nitrogen is 30, urea nitrogen 6.9, and uric acid

\*The examination was made on a three-hour specimen obtained by catheterization after a fifteen-hour fast. No attempt was made to determine the total number of casts, epithelial cells, leucocytes, erythrocytes, etc., for twenty-four hours, but the average number of these various formed elements was determined in two low-power fields. If the number was small then eight fields were counted.

4.3. If these figures are correct the undetermined nitrogen is markedly increased. They report blood urea nitrogen of 2.8, 3.6, 4.5, 4.6, etc., with nonprotein nitrogen determinations on the same patients of 27, 25, 30, 20. In the group classed by them as chronic nephritis, the inconsistency is even greater.

The nonprotein nitrogen and blood urea nitrogen are diminished early in pregnancy and the decrease persists throughout. We have studied the same women throughout pregnancy and the puerperium and found that the average nonprotein nitrogen in the three trimesters was 25, 25, and 24 mg. per cent, respectively. In the first postpartum week it was 28, and in the second, 29 mg. per cent. We have no adequate explanation for the decrease in the nonprotein nitrogen or blood urea nitrogen. It is obviously not due to the passage of urea into the amniotic fluid because of its occurrence so early in pregnancy. However, we wish to point out that since the blood urea is the divisor in determining the U/B ratio, any lowering of it, whether real or artificial (error in method), will not only increase the U/B factor but also the clearance.

In Table IV are listed the means for the urea concentration factor. Rabinowitch stated that if 15 gm. of urea were given by mouth after an all-night fast, and blood and urine urea determined in one and two hours, the quotient derived by dividing the urine urea nitrogen by the blood urea nitrogen was an excellent indication of renal function. In normal individuals the mean was 47.3, with a standard deviation of 6.9. This factor forms part of the clearance equation, and since our clearances were obtained with restricted fluids, we have calculated the U/B ratio and believe it is of value. In normal pregnancy the range is from 9 to 119, mean 63.8, and the standard deviation is 32.6. This high figure is explained by the decrease in blood urea.

Since the Leiboff acid hydrolysis method with blood usually gives 1 or 2 mg. per cent more than the other methods, and the results with urine are essentially the same, then our figures for U/B and for the clearance should be slightly less than those based on other methods. However, to our surprise, in normal pregnancy, despite the tremendous range, the extremely high means of 63.8 before and 71.5 after delivery were found. With an average blood urea nitrogen of 6.9, as reported by Hurwitz, in contrast with our average of 12 mg. per cent, the urea concentration factor would be still higher. The means for Groups I, II, and III before delivery, despite the normal blood urea, are decidedly below the normal for pregnancy. This reduction is due entirely to the decrease in the concentration of the urine urea. We do not know whether this low concentration of urine urea before delivery is the result of renal damage, vascular spasm of the glomerular vessels causing decreased elimination, or of increased absorption of urea

in the tubules. In Group I the difference between the antepartum and postpartum means is of no significance. In Group III the difference is of significance and is especially low before delivery. It should be pointed out that most of our deaths have occurred in this group, in which there is no history of previous toxemia or cardiovascular renal disease. It should also be emphasized that despite the increase in the

TABLE IV. UREA CONCENTRATION FACTOR—VARIATIONS AND AVERAGE

U/B FACTOR	NORMAL PREGNANCY		NONCONVULSIVE TOXEMIA						ECLAMP- SIA	ABRUP- TIO PLA- CENTAE
			GROUP I PRE- ECLAMPSIA		GROUP II HISTORY OF TOXEMIA		GROUP III NO HISTORY OF TOXEMIA			
	A.P.	P.P.	A.P.	P.P.	A.P.	P.P.	A.P.	P.P.	P.P.	P.P.
1- 9	1							3	1	4
10- 19	1		3	1	4	4	6		2	4
20- 29	2		6	5	8	4	6		7	8
30- 39	3	1	6	11	8	6	6	7	7	8
40- 49	4	3	7	7	5	8	2	5	5	1
50- 59	1		1	3	2	6		2	3	0
60- 69	1	1		1	4	2		1	1	1
70- 79	5	2	1		3			1		
80- 89	3			1	1	1	1	2		
90- 99	3									
100-109		1								
110-119	3	2								
Total	27	10	24	29	35	31	21	21	26	26
Mean	63.8	71.5	34.9	39.1	40.8	40.6	29.3*	42.6*	34.5	35.3
Standard deviation	32.6	29.8	13.6	14.9	20.4	16.9	16.3	22.0	14.0	13.6
Probable error	4.33	6.36	1.87	1.97	2.33	2.05	2.40	2.24	1.85	1.80

\*Significant difference.

blood urea nitrogen, the U/B quotient is higher after than before delivery in Groups I and III. After eclampsia and abruptio placentae the quotient is slightly decreased, but not enough to indicate definite renal impairment.

In Table V are listed the variations and means for the Van Slyke urea clearance. All clearances are expressed as percentage of normal and are calculated as the standard, with but few exceptions. In the nonpregnant individual the standard clearance ranges from 40 to 68 c.c. (74 to 126 per cent), with an average of 54 c.c. (100 per cent) of blood, and the maximum clearance ranges from 65 to 103 c.c. (85 to 135 per cent), with an average of 76 c.c. (100 per cent) of blood. In 19 clearances on the author since 1930, the range has been from 43 to 170 per cent. On Dec. 11, 1933, and Feb. 8, 1934, hourly clearances with almost constant urine volumes were 130, 105, and 78 per cent, and 110, 120, 96, 128, and 115 per cent, respectively. However, it has been stated by all observers that one characteristic of the normal kidney is its marked variability in contrast with the impaired kidney

which shows constant low values. In normal pregnancy the mean is 102.3 per cent, with a standard deviation of 30.9. It is higher after delivery despite the increase in the blood urea, because both the urine urea concentration and the urine volume are increased.

TABLE V. UREA CLEARANCE, VARIATIONS AND AVERAGES

PER CENT	NORMAL PREGNANCY		NONCONVULSIVE TOXEMIA						ECLAMP-SIA	TIO ABRUP-PLA-CENTAE
			GROUP I PRE-ECLAMPSIA		GROUP II HISTORY OF TOXEMIA		GROUP III NO HISTORY OF TOXEMIA			
	A.P.	P.P.	A.P.	P.P.	A.P.	P.P.	A.P.	P.P.	P.P.	P.P.
10- 19					1		2	2	2	
20- 29			2	2	1		5	4	1	
30- 39			5	1	5	4	9		4	3
40- 49	1		4	1	8	6	1	5	3	3
50- 59	2	1	7	6	7	3	4	6	4	6
60- 69			4	8	3	5	2	1	3	9
70- 79	3		3	5	3	3	1	1	4	3
80- 89	5			2	4	3		2	3	1
90- 99	1	1			1	3		2	1	1
100-109	5	2		2	2			1	1	
110-119	2	2								
120-129	4					1				
130-139		1				3				
140-149	2									
150-159	1									
160-169										
170-179	1	3								
Total	27	10	25	27	35	31	24	24	26	26
Mean	102.3	124.5	50.5	63.2	57.4	64.5	38.7*	53.2*	57.2	56.4
Standard deviation	30.9	39.2	15.2	19.9	22.0	30.5	16.3	23.9	24.0	15.3
Probable error	4.01	8.36	2.05	2.74	2.51	3.69	2.24	3.29	3.18	2.02

\*Significant difference.

In the nonconvulsive group, all of the clearances were greater after delivery than before, but Group III was the only one in which the increase was significant. Since the clearance before and after delivery was obtained on the same patient, it is evident that pregnancy does cause a decrease which, in Groups I and II, is due primarily to a diminished volume of urine per minute, but in Group III there is, in addition, a decreased concentration of urea. The means for the clearance in patients who had either eclampsia or abruptio placentae are 57.2 and 56.4 per cent, respectively. All of the means in the toxemic patients after delivery are less than 65 per cent.

In Groups I, II, and III, 44, 43 and 71 per cent, respectively, of the clearances are less than 50 per cent before delivery, and 15, 32, and 46 per cent after delivery. In the groups of patients in whom eclampsia or abruptio placentae occurred, 38 and 23 per cent, respectively, of the clearances are below 50 per cent.

Our purpose in using the clearance test was to determine its value in pregnancy as an aid in differential diagnosis and prognosis. One difficulty encountered in properly interpreting its values is that the range for the normal nonpregnant individual is still too great because of the relatively few observations that have been made. It is obvious that the urea clearance is of little value in pregnancy in the majority of cases as an aid in diagnosis or prognosis. After delivery it is of value in determining if the kidney function has returned to normal, but it does not aid very much in determining whether or not the patient has nephritis. If the clearances are all low and there is no marked pathology of the cardiovascular system, it then indicates that the amount of functioning kidney tissue is decreased.

#### COMMENT

Spalding, Shevky and Addis, in 1922, stated that their results suggested the possibility of an increase in the amount of effective kidney substance during pregnancy, and that the decrease in the ability of the kidneys to excrete urea in toxemic patients was a real decrease and was not due to the pregnancy itself. In three patients with marked renal impairment, they suggested that the chronic kidney lesion might have had its origin in an unhealed nephrosis contracted during a toxemia of pregnancy. They also noted, especially in toxic patients, a tendency toward an oliguria. They concluded that, provisionally, the renal lesion in the toxemia of pregnancy was important not before, but after, delivery.

Hurwitz and Ohler reported clearances in 21 toxemic patients and stated that in 13 the clearance was normal and in 8 it was less than normal. The average was 111 per cent. In 17 patients with chronic nephritis they found three with normal and 14 with low clearances. The average was 64 per cent. The average clearance in five patients after eclampsia was 61 per cent. In five normal pregnant patients the average clearance was 127 per cent. They concluded that the urea clearance checked up well with the clinical diagnosis, in that it was normal in the toxemias, decreased in the acute stage of eclampsia, and low with a high degree of consistency in chronic nephritis. They also stated that their data suggest a correlation between the unusually high urea clearance and the low blood urea nitrogen in normal pregnancy. The comparatively high figures for the clearance may be due to the low blood urea nitrogen, for which their average was 6.9 in the toxemic, and 9.8 mg. per cent in the nephritic, group.

Cantarow and Ricchiuti, in a study of the urea clearance in pregnancy, stated that in 39 normal pregnant women, the urea clearance values ranged from 28 to 184 per cent; the average was 71.5 per cent (54 c.c. = 100 per cent). The urea clearance which was normal early in pregnancy diminished as pregnancy progressed, being rather consistently low a few days before the onset of labor. Subnormal clearance values obtained during the last two months of gestation must be interpreted with extreme caution, particularly in the absence of clinical or laboratory evidence of renal dysfunction.

Stander and coworkers, in 1932, used various renal functional tests in the toxemias and concluded that the urea clearance, guanidine and creatinine excretion tests were of real value in the differentiation between mild nephritis and the other toxemias of pregnancy. They stated that a urea clearance below 80 per cent is strongly indicative of renal damage. Since the first publication, Stander has become more cautious in interpreting the urea clearance, and in a recent report states as follows: "Any urea clearance which gives values below 50 per cent is very strong proof of the existence of a chronic nephritis. A urea clearance above 50 per cent does not necessarily mean that the patient does not have chronic nephritis, and in these cases it is necessary to study the patient further."

The fact that the various renal functional tests do not show marked kidney impairment after the toxemias of pregnancy does not mean that they should be discarded. The diagnosis of preeclampsia or eclampsia, primary or secondary hypertension, nephrosis, acute or chronic glomerulonephritis should be based on the history, physical examination and *repeated* examinations of blood, urine, and kidney function. Thus a patient with a persistent hypertension after delivery, but with normal or low normal renal function, would be diagnosed as having primary hypertension or hyperpiesia. However, we believe that pregnancy can be the etiologic agent in causing the hypertension and, if so, the diagnosis then would be secondary hypertension. This point requires further investigation. Similarly, the patient in whom the urea clearance is (1) persistently below 50 per cent; (2) the maximum specific gravity of the urine is 1.015 or less; (3) the Addis count reveals an abnormal increase in formed elements, or (4) any standard renal functional test showing a significant decrease, would be diagnosed as having renal impairment. This condition might have as its etiology an acute glomerulonephritis, a primary hypertension, with renal impairment due to nephrosclerosis, a pyelitis and hydro-nephrosis with destruction of kidney substance, a preeclampsia or eclampsia, or an abruptio placentae. Only by careful observations and repeated blood and urine studies in these toxemic patients over a period of years can the various diseases be satisfactorily explained and classified.

#### CONCLUSIONS

##### *In Normal Pregnancy.*—

1. The means for the blood nonprotein nitrogen and urea nitrogen which are 23.8 and 12.2 mg. per cent, respectively, are below normal.
2. There is a delayed or decreased elimination of water by the kidney.
3. The concentration of urea and NaCl in the urine is decreased and, therefore, the mean for the maximum specific gravity of the urine is 1.022.
4. The mean for the urea concentration factor is 63.8 before and 71.5 per cent after delivery. This increase above the normal is caused by the reduction in the blood urea.

5. The mean for the urea clearance is 102.3 before and 124.5 per cent after delivery.

6. The urea clearance, despite the decrease in the blood urea, is apparently decreased in the last half of pregnancy, if studied in individual patients.

*In the Toxemias of Pregnancy.*—

1. The averages for the blood nonprotein nitrogen and urea nitrogen are 30.6 and 14.5 mg. per cent, respectively. In the absence of a hypochloremia or an oliguria, a nonprotein nitrogen of 40 mg. per cent or more, or a urea nitrogen of 20 mg. per cent or more, should always suggest renal impairment. Patients with sufficient kidney pathology to cause a nitrogen retention as a rule either do not conceive or if they do, death of the fetus or mother usually occurs early in the pregnancy.

2. The urinary excretion of water is even more markedly decreased than in normal pregnancy. This delayed or retarded water elimination may be due to an arteriolar spasm of the renal vessels, thus diminishing the glomerular filtrate, or to increased reabsorption of water in the tubules. Lack of water in the blood stream (hemoconcentration), because of the increased permeability of capillary and cell walls due to the toxemia, may also be a factor.

3. The concentration of urea and NaCl in the urine is still further decreased, thus resulting in an average specific gravity of 1.018 before and 1.020 after delivery.

4. The mean for the urea concentration factor is slightly less than that given for the nonpregnant individual. It is approximately one-half of the mean for the normal pregnant patient.

5. The urea clearance test in patients with toxemia, hypertension, or nephritis, as a rule, is definitely decreased during the latter half of pregnancy. This impairment is caused by the reduction or delay in the elimination of water and the diminished concentration of urea in the urine.

6. A urea clearance after delivery, which is persistently 50 per cent of the normal or less, indicates renal impairment. This organic renal change may be the result of preeclampsia, eclampsia, nephrosclerosis, glomerulonephritis, or of pyelonephritis.

7. Many patients, over a period of three to six months after delivery, show considerable increases in the clearance. The phenomenon may be explained by assuming an hypertrophy of the remaining kidney tissue, or a slowly decreasing arteriolar spasm of the renal vessels, thus permitting more filtration. Therefore, renal functional tests for diagnostic value should be performed weeks, or preferably months, after delivery.



8. The Addis count is of considerable value in differentiating the various types of toxemia during pregnancy.

9. Careful observations and *repeated* studies of the blood, urine, and renal function over a period of years in a large number of toxemic patients are essential for a proper classification.

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**Khreninger-Guggenberger and Leutenmayer**: Primiparae in the Fifth Decade of Life, Arch. f. Gynäk. 154: 309, 1933.

The incidence of primiparas more than forty years old has increased in Germany since the World War. The authors report on 151 such patients delivered in the Munich Frauenklinik. They found among them a higher incidence of contracted pelvis with a correspondingly high morbidity and mortality. Another serious complication in this group is the high rate of cardiac disease; there was no increased incidence of renal disease; eclampsia was not encountered. Apparently the percentage of women carrying to term decreases as the age increases since one out of every six in this group had a premature labor.

The duration of labor during the fifth decade is no greater than in the fourth decade; labor lasted longer than twenty-four hours in one out of four, and longer than two days in one out of every 27. Premature rupture of the membranes occurred once in every 3.5 patients. Every third labor was terminated by operative delivery; one in six by forceps.

The fetal mortality is high, there being one death in every 5.5 deliveries.

RALPH A. REIS.

**Macchiarulo, O.**: A Case of Primary Echinococcus Cyst Infestation of the Uterus, Folia gynec. 31: 89, 1934.

After a review of the few cases of echinococcus cyst infestation of the uterus reported in literature, the author describes a case of primary infestation of the uterus observed by him. He concludes that the only rational treatment is hysterectomy.

MARIO A. CASTALLO.

## A CLINICAL COMPARISON OF VARIOUS ERGOT PREPARATIONS ON THE POSTPARTUM HUMAN UTERUS

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CONSIDERABLE experimental work has been done on the effects of various extracts as well as of a number of pure drug principles derived from the fungus ergot on the uterus of animals both in vitro and in situ. However, comparatively few controlled observations have been made on the gravid or postpartum human uterus in situ. The published reports of these observations are somewhat conflicting, due probably to the different methods of study which have been used.

The modern study of ergot began in 1906 when Barger and Dale<sup>1</sup> isolated an alkaloid in pure crystalline form which they called ergotoxine. Previous to this time, however, because of impure chemical preparations, no active principle of ergot had been isolated. Ergotoxine was found to be highly active, and, under experimental conditions, produced all the typical pharmacologic actions of ergot. It also proved to be closely related to Tanret's ergotinine isolated in 1875 but found to be inert. Ergotoxine, prepared by the Burroughs Wellcome and Company, was considered the specific alkaloid and most active principle of ergot until 1921 when Stoll of the Sandoz Laboratories isolated ergotamine which he claimed to be a crystalline compound of slightly different composition than ergotoxine. The correspondence between Stoll and Dale in which the problem of recognition of their respective products as the specific alkaloid of ergot was discussed, appeared in *Lancet*<sup>2</sup> in 1930. More recently, others<sup>3</sup> have published work indicating that ergotoxine and ergotamine are equivalent as to pharmacologic action although slightly different chemically. Moir<sup>4</sup> observed no clinical differences between these products. During the last year, two entirely new alkaloids of ergot have been isolated by American drug firms and made available for clinical trial. We feel that the state of our knowledge of the clinical effectiveness of the various ergot preparations is still incomplete, particularly from the standpoint of quantitative reactions, as well as the relative duration of action on the postpartum uterus.

The U.S.P. fluid extract of ergot is generally considered to be the most reliable of the series of drugs available for limitation of postpartum hemorrhage and acceleration of involution of the uterus. However, the B.P. liquid extract continues to be used in England although some<sup>5</sup> have cast doubt on the efficiency of this preparation in that it was reported to be devoid of alkaloids. Carr and Dale<sup>6</sup> criticized the methods used for preparing the liquid extract in that ergotoxine was thus eliminated. Bourne and Burn<sup>5</sup> concluded that the B.P. liquid extract was clinically inert due to the small amount of alkaloids present. These authors compared the effectiveness of different ergot preparations by observing the rate of uterine involution during the postpartum period. Moir,<sup>7</sup> however, studied the reaction of the postpartum uterus to a series of ergot preparations (using the bag induction technic) and found the reactions to the B.P. liquid extract of ergot to be more rapid and of greater magni-

tude than that obtained with any drug previously used. This reaction was ascribed to an unknown active principle in that he considered his liquid extracts as being alkaloid-free; thus the oxytocic reaction could not be due to ergotoxine, ergotinine, histamine, or tyramine.

The present study was undertaken in order to clarify the conflicting reports as to the relative clinical efficiency of the B.P. liquid and the U.S.P. fluid extracts of ergot. It has been supplemented by a comparison of the reaction of the postpartum uterus to ergotoxine, gynergen, ergot aseptic, histamine, tyramine, pituitrin, and morphine.

#### METHODS

Two methods have been utilized for the study of the postpartum human uterus in situ, i.e., the insertion of a bag into the uterus and recording uterine motility by changes in hydrostatic pressure as described by Bourne and Burn,<sup>5</sup> Moir,<sup>7</sup> Adair and Davis,<sup>8</sup> and the indirect or abdominal tambour method first used by Rubsamen<sup>9</sup> in 1913.

The hydrostatic bag method has certain advantages in that very fine movements of the uterus are recordable, which might be insufficient in degree to be indicated by the indirect records of uterine movements as obtained from the abdomen. Further, the position of the uterus would not significantly alter the type of record obtained directly, whereas changes of position of the uterus are of significant importance when motility is observed by the indirect method. On the other hand, the uterus reacts to the presence of the bag as to a foreign object, and the motility due to the distensive stimulus probably is of abnormal type. The use is limited to the sixth or seventh postpartum day or after low cervical cesarean section, and is attended by the danger of infection.

The method used in the present report is that described by Dodek<sup>10</sup> with the exception of a minor modification of the abdominal tambour. The apparatus consisted of a delicate abdominal tambour which was supported in an upright position by a metal tripod strapped firmly to the patient's abdomen by means of adhesive tape. This tambour was placed so that the button at the end of the recording lever firmly contacted the abdominal wall directly over the dome of the uterine fundus. Movements of the uterus were transmitted by air pressure from the abdomen to a second tambour, the excursions of which were recorded in ink on a clock-driven paper. This method may be used during the course of labor or repeatedly at any convenient time during the postpartum period. Patients were not subjected to pain or discomfort during the course of a record of uterine movements, but were required to remain quiet with minimal muscular movements for approximately two hours. The limitations of this procedure necessitate choosing patients with moderate to thin abdominal walls for optimal records. Patients were encouraged to void urine before beginning a tracing, as a full or rapidly filling bladder predisposed to restlessness, and, in addition, tended to alter the position of the uterus with resulting errors in the graphic records. For the same reason, the routine castor oil, as administered in this hospital, was not given if uterine tracings were to be made on the first postpartum day. The reactions to various medicinal agents as observed by the indirect method compare very closely with those obtained by the bag induction method. The indirect method, therefore, appears to offer a safe and reliable clinical assay procedure for various oxytocic agents useful during the third stage of labor or the postpartum period. In addition, the type of uterine activity is helpful in judging the rate of involution.

## RESULTS

Uterine movements are most active shortly after delivery, but quite regular optimal reactions are obtainable by the indirect method used during the first four postpartum days. Our data were obtained from

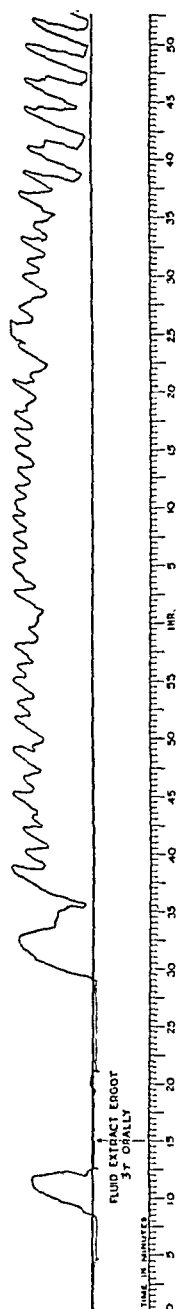


Fig. 1.

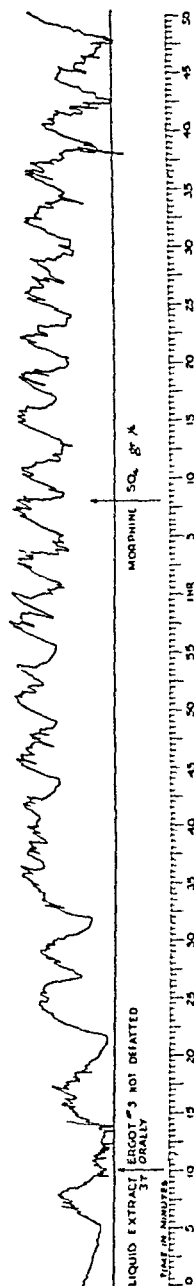


Fig. 2.

one hour after delivery to the fourth postpartum day, but, as a rule, records were obtained on the first or second postpartum day because of greater convenience. At this time, patients have completely recovered from any premedication sequence or anesthesia and are more comfortable and cooperative.

The routine of an experiment was as follows: a control tracing of the uterine movements was obtained over a forty-five-minute period, after which the drug selected for testing was administered and continuous tracings obtained during the subsequent sixty to ninety min-

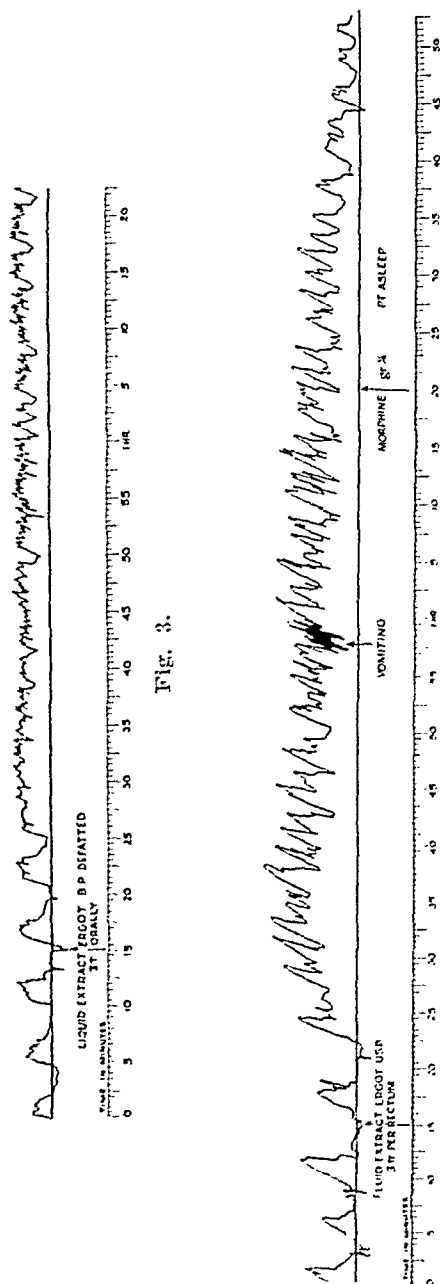


Fig. 3.

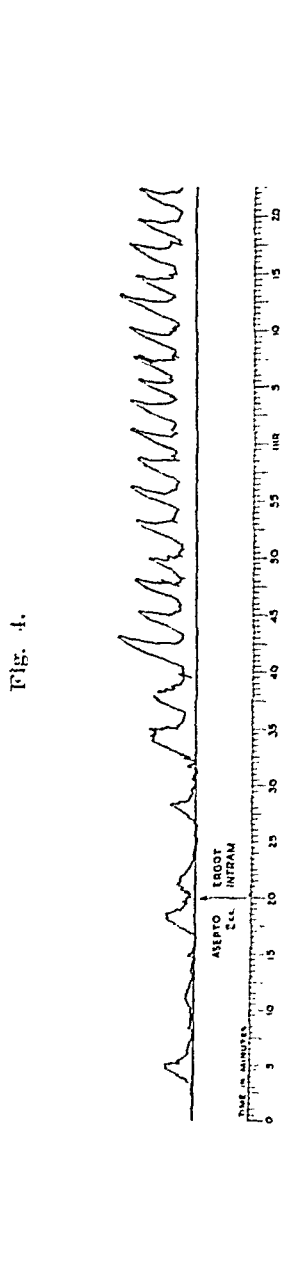


Fig. 4.

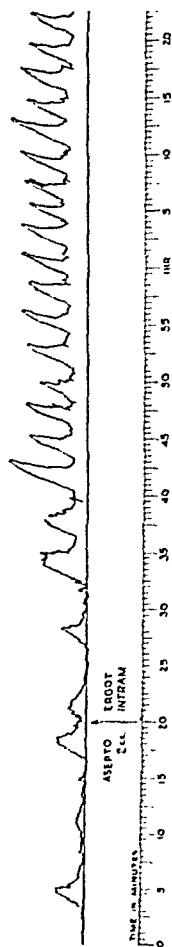


Fig. 5.

utes. The duration of action of certain of the agents tested was checked by later tracings on the same patient.

The uterine responses of individual patients were of the same order in that rhythmicity and contractility were maximal shortly after delivery and gradually diminished with time after delivery. However, the recorded responses of different patients varied widely so that ac-

curate measurements of the responses for purposes of comparison appeared impractical. The time of reaction was recorded accurately but changes in frequency, contractility, and tone were tabulated as plus, minus, or no change. The percentile frequency of these reactions has been used for illustration. More detailed differences will be discussed in the text.

The reaction of the uterus to ergot administered by different routes is indicated in Table I. This illustrates the time and frequency of reaction to the U.S.P. fluid extract and the B.P. liquid extract administered orally, Parke, Davis and Co. ergot aseptic intramuscularly, and to the U.S.P. fluid extract rectally.

TABLE I

METHOD	DRUG	DOSAGE (C.C.)	REACTION TIME (MINUTES)		PER CENT SHOWING INCREASES			EFFICIENCY* HIGH (1) TO LOW (4)
			MIN.	MAX.	FR.	HT.	TONE	
Oral	U. S. P.	4	12.0	25.0	100	70	90	2
Oral	B. P.	8	11.5	25.0	100	100	100	3
Intramuscularly	P. D. & Co. aseptic	2	9.5	25.0	100	50	100	4
Rectal	U. S. P.	8	7.5	22.5	100	100	100	1

\*Estimated by the degree and duration as well as by the frequency of stimulation.

The uterine response to preparations of ergot is somewhat more erratic after oral than after intramuscular injection of ergot aseptic or the rectal instillation of the U.S.P. fluid extract due to differences in the rate of absorption and occasional nausea and emesis. The rectal administration of the fluid extract (diluted with two to three volumes of water) offers certain advantages in that the injection may be made immediately after delivery, nausea or emesis is not encountered, and the uterine stimulation occurs more promptly and is greater in degree than after oral or intramuscular injections of ergot. Ergot aseptic was next most regular as to the uterine responses obtained. The intramuscular injection offers certain advantages in that medication can be given immediately after completion of the third stage of labor. However, the degree of response was distinctly less than in the case of either the fluid or liquid extracts on oral administration. The observed differences are quite probably due to the minimal dosage of the aseptic injected, but the danger of infection is present and conscious patients complain of pain. The psychic reaction to the pain of such injections is reflected by a significant depression of uterine motility for ten to twenty minutes.

The dosages of the ergot preparations used varied from 2 to 8 c.c. A maximum dose of the fluid extract (4 c.c.) produced such disagreeable uterine cramps that in later observations 2 c.c. dosages were used.

The reactions obtained from this minimal dose were grossly comparable to those obtained with a 4 c.c. or drachm dose of the liquid extract.

The uterine reaction to small or medium dosages of ergot is reflected by an increased frequency and height of contraction with a moderate increase in tone. With maximal dosages, a spastic or tonic reaction occurs in that the tone rises maximally, and the uterus remains firmly contracted for twenty-five to forty-five minutes. The latter type of contraction is quite painful and patients become restless and complain. The two reactions are the same and differ only quantitatively and are modified partly by the irritability of the uterus but primarily by the dosage administered.

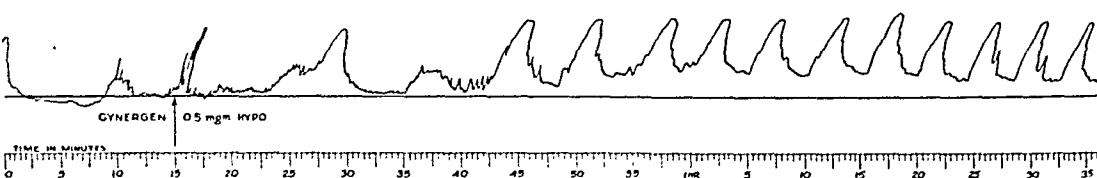


Fig. 6.

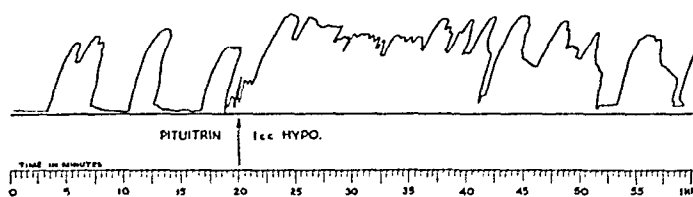


Fig. 7.

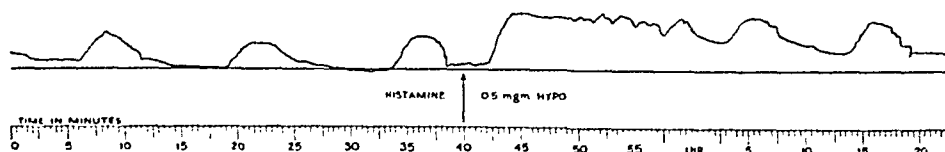


Fig. 8.

The influence of age on the rate of deterioration of both the U.S.P. fluid extract and the B.P. liquid extract was observed by making clinical tests of the potency of standard dosages of the preparations obtained from the same stock of crude ergot over a period of twelve months.

The U.S.P. fluid extract and the B.P. liquid extract (defatted and not defatted) were prepared and assayed chemically by Mr. E. D. Davy of the School of Pharmacy from a high grade Spanish (rye) ergot obtained through the courtesy of Dr. E. H. Volwiler of the Abbott Laboratories. A sufficient supply of these preparations was made to permit correlation of the clinical tests and the alkaloidal content of the extracts over a twelve-month period. In addition, the clinical effectiveness of the alkaloids (diluted to comparable volumes) obtained

from both the U.S.P. and B.P. extracts was compared with that observed with the alkaloid-free extracts.

The ergot preparations were made in November, 1932, and assayed in December, 1932, by the colorimetric method of M. I. Smith. The alkaloid content as compared with a standard ergotamine ethanesulphonate solution at that time is as follows:

Fluid extract of ergot U. S. P.	5.38 mg. alkaloids per 10 c.c.
Liquid extract of ergot B. P. (not defatted)	1.60 mg. alkaloids per 10 c.c.
Liquid extract of ergot B. P. (defatted)	1.44 mg. alkaloids per 10 c.c.

The relative clinical effectiveness of the U.S.P. fluid extract and the B.P. liquid extract over a period of one year together with the

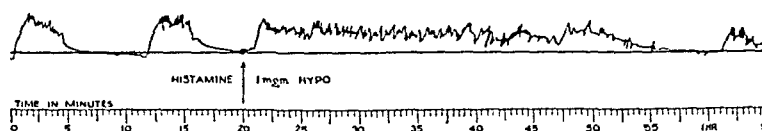


Fig. 9.



Fig. 10.

chemical assay of the alkaloids contained is illustrated in Table II. Deterioration according to the chemical assay method was very rapid and was complete so far as the limits of the colorimetric methods indicated within one year, at which time the preparations were stimulant to the uterus although the potency was reduced at least 75 per cent. The reaction of the uterus to the aged preparations was greatly

TABLE II

DATE	DRUG	(MG.) ALKALOIDS IN 10 C.C.	REACTION TIME (MINUTES)		PER CENT SHOWING INCREASES		
			MIN.	MAX.	FR.	HT.	TONE
Dec., 1932	U. S. P. fluid extract (E. D. Davy)	5.38	12	25	100	70	90
June, 1933	U. S. P. fluid extract (M. I. Smith)	0.75	27	35	100	0	0
Nov., 1933	U. S. P. fluid extract (E. D. Davy)	0.00	47	70	100	100	0
Dec., 1932	B. P. liquid extract* (E. D. Davy)	1.60	11.5	25	100	100	100
June, 1933	B. P. liquid extract (M. I. Smith)	0.30	55.0	78	100	100	0
Nov., 1933	B. P. liquid extract (E. D. Davy)	0.00	42.5	70	100	0	0

\*The liquid extract was not defatted.



delayed as to the time of development and was limited to an increase in frequency with a slight increase in the amplitude of contraction. No increase in tonus was observed.

We are unable to explain the discrepancy between the observed clinical effectiveness of the aged ergot preparations and the theoretical potency as indicated by the absence of alkaloids. Samples of the official U.S.P. and B.P. preparations were sent to Dr. M. I. Smith of the U. S. Public Health Department in May, 1933. The possible upper limits of their alkaloidal contents as observed by Dr. Smith are indicated in the table. He reported that the preparations should be clinically inert. It is imaginable that the active principles, if due entirely to alkaloids, may have become altered in some manner during deterioration, so that although some activity remained, the principles were not detectable by the chemical assay method.

#### IS THE OXYTOMIC ACTIVITY OF ERGOT DUE TO ALKALOIDS ALONE?

Bourne and Burn compared the efficiency of a series of ergot preparations by noting the influence of these agents on the rate of uterine involution (as judged by the height of the fundus above the pubis) during the postpartum period. The B.P. liquid extract was considered inert. Moir observed the uterine responses (by the bag induction method) to both the U.S.P. and B.P. extracts as well as to other oxytomic principles, and concluded that the reactions to the B.P. liquid extract were more rapid in development and of greater amplitude than the responses to any other agent tested. This activity was ascribed to a new hypothetical principle (nonalkaloidal in character) and not attributable to histamine. His analysis of the liquid extract indicated that it was alkaloid-free.

The clinical efficiency of our U.S.P. and B.P. extracts together with the reactions to the alkaloids (from the B.P. extract) alone and the alkaloid-free B.P. extract is illustrated in Table III.

The alkaloids were removed from the liquid extract with ether in an automatic extractor, after evaporating the alcohol and rendering

TABLE III

DRUG	DOSE (C.C.)	ALK. PER 10 C.C. (MG.)	REACTION TIME (MINUTES)		PER CENT SHOWING INCREASES		
			MIN.	MAX.	FR.	HT.	TO NE
(1) Fluid extract ergot U. S. P.	4	5.38	12.0	25	100	70	90
(2) Liquid extract ergot B. P. d.f.*	8	1.44	13.0	20	100	84	100
(3) Liquid extract ergot B. P. n.d.f.*	8	1.60	11.5	25	100	100	100
(4) Pure alkaloid soln. from No. 3	8	1.60	20.0	28	100	66	66
(5) Alkaloid-free soln. from No. 3	8	0.00	26.0	35	60	40	0

\*d.f., defatted; n.d.f., not defatted.

the residue alkaline with ammonia. Extraction was continued for four hours, after which a negative test for alkaloids was obtained. The residue was acidified slightly with hydrochloric acid, the ether dispelled and the product diluted with alcohol to the original volume of the liquid extract. The same procedure was followed in handling the alkaloids represented in the ether extractive.

Table III illustrates the median results from a series of 30 patients who had been given the various ergot preparations by mouth. The B.P. nondefatted liquid extract appeared somewhat more efficient than the defatted extract. The difference in alkaloid content is not very great but probably enough to account for the differences in stimulation. On a dose basis, the B.P. ergots appeared about one-half as active as the U.S.P. fluid extract. One important difference observed was the lower frequency of spastic (painful) uterine reactions to the liquid extract. However, the activity of this preparation was greater than might be expected on the basis of its alkaloid content, in that the U.S.P. fluid extract on the same basis should be approximately three times as active as the B.P. extract. This discrepancy might be explained in several ways. First, the uterus probably reacts maximally to a given dose of alkaloid, and any more than this quantity has no further effect. We assume that our dosages were maximal in most patients studied. This is again emphasized by the fact that after the uterus had reacted to a maximal dose of ergot, the administration of a second dose within two to two and a half hours after the first dose was not followed by a significant further stimulation. Blair-Bell<sup>15</sup> in his studies on pituitrin observed that the initial injection produced marked uterine contractions and a rise in tone; but, as with a second dose of ergot, subsequent injections of pituitrin produced minimal or no reactions unless a certain interval of time (one to two hours) was allowed to elapse between the first and second doses. The state of irritability of the uterus and particularly the nature and time of previous medication is of significant importance so far as clinical assays are concerned.

A second possibility is that the standard assay methods (chemical and biologic) do not give a wholly satisfactory index of the clinical efficiency of the ergot preparations. Comparison of the stimulant properties of the total alkaloids from either of the official pharmacopeial preparations with that of the original products indicated the greater potency (35 per cent) of the original extracts. However, the original extracts rendered alkaloid-free according to chemical tests by extraction of these principles continued to produce a slight stimulation of the uterus. No explanation is offered as to why the original extracts were of greater potency than the alkaloids contained in them, or that the alkaloid-free extracts retained a slight activity. Our observations do not confirm those of Bourne and Burn in that the B.P.

an increase in frequency and height of the individual contractions over the control curve. Stimulant effects persisted for approximately 1.5 hours.

The influence of therapeutic dosages of morphine on the postpartum uterus was noted in a group of patients previously medicated with maximal dosages of ergot. This narcotic was administered in  $\frac{1}{4}$  grain dosages subcutaneously to relieve the discomfort due to marked tonic uterine contractions. Such dosages promptly relieved the patients, but, in addition, the uterine tone decreased gradually to normal within twenty to thirty minutes, and in several cases motility and tone became definitely subnormal, and this was accompanied by an increased uterine blood loss. These data indicate the important relationship which exists between impulses from the central nervous system and uterine motility, and suggest that morphine should be administered cautiously during the early postpartum period because of the possible loss of uterine tone with a resultant increase in the postpartum hemorrhage.

#### SUMMARY AND CONCLUSIONS

1. The clinical efficiency of extracts of ergot as judged by the reaction of the postpartum uterus differs significantly according to the mode of administration; so far as the speed of reaction is concerned, the order is rectal, intramuscular, and then oral. However, the maximal differences in point of time ranged from 7.5 to 12 minutes with the three routes of administration. The order of magnitude and duration of response has the following order from the greatest to the least: rectal, oral U.S.P. fluid extract, oral B.P. liquid extract, and ergot aseptic intramuscularly. The difference of reaction efficiency between intramuscular and oral routes of administration is possibly a matter of dosage. The intramuscular injection may be given at any time during the postpartum period and nausea and vomiting do not occur, but the chance of infection is always present and the patient is subjected to pain. The rectal administration of the fluid extract (diluted with 2 to 3 volumes of water) produces optimal reactions and has the same advantages of intramuscular injections, and none of the disadvantages of either oral or intramuscular injection. The rectal administration appears to be the route of choice.

The maximal effects of the crude drug principles persist for forty-five to ninety minutes, and stimulation is still apparent up to four hours after oral or rectal administration. Responses to second dosages within two hours are negligible. The dosage frequency should not exceed every three to four hours.

2. The B.P. liquid extract of ergot is approximately one-half as effective as the U.S.P. fluid extract. The rate of absorption on oral administration is almost exactly the same as for the U.S.P. preparation. The B.P. liquid extract contains significant quantities of alkali-

loids but slightly less than one-third of the quantity present in the U.S.P. fluid extract made from the same crude ergot. The activity of both preparations is primarily, but not entirely, dependent on the alkaloidal content of the extracts as indicated by the chemical methods of assay.

3. Aging of the U.S.P. fluid extract results in a deterioration of approximately 85 per cent on the basis of chemical tests for alkaloids in a period of eight months, although the clinical efficiency decreased not more than 50 per cent during the same period of time. The alkaloidal tests of either the U.S.P. or B.P. extracts after one year were negative. Nevertheless, these alkaloid-free solutions retained a clinical activity equivalent to 15 to 25 per cent of the original potency. The B.P. extracts deteriorated at approximately the same rate as the U.S.P. preparation of ergot (alkaloidal basis) and likewise exhibited a slight clinical activity at the end of one year. We are unable to explain the discrepancy between the chemical tests for alkaloids and the observed clinical tests after twelve to fourteen months' aging. There is a possibility that the active principles may have been altered in some manner during the deterioration, so that they were not detectable by the chemical assay methods used.

4. Ergotamine tartrate (gynergen) and ergotoxine ethanesulphonate produce changes in the postpartum uterus of the same character and order of magnitude. These principles administered hypodermically or intramuscularly are absorbed more slowly, and in dosages free of undesirable side actions (nausea, emesis, etc.), are distinctly less effective than the crude drugs administered by rectal, oral, or intramuscular routes.

Histamine in a dosage of 0.5 mg. hypodermically produces a tonic contraction of the uterus within one to two minutes. The spastic reaction diminishes gradually and disappears within thirty to thirty-five minutes after the injection. Larger doses, because of undesirable circulatory and general smooth muscle reactions, do not appear advisable. When the relatively negligible differences in speed of reaction and more particularly the duration of action are considered, the crude drug principles are to be preferred.

The administration of tyramine in maximal therapeutic dosages produces a slight increase in the height of uterine contractions but reactions are inconstant and the effectiveness may be considered unimportant.

Pituitrin hypodermically in maximal dosages results in a marked increase in the tonicity of the postpartum uterus within three to six minutes. The effects gradually diminish from the early peak and disappear within forty-five to ninety minutes. Second dosages are relatively ineffective if injected earlier than forty-five minutes after the initial dosage. The postpartum uterine response to pituitrin is

directly proportional to the dosage administered. Small dosages produce a moderate rise in tonus and significant increases of the frequency and amplitude of contractions. Maximal dosages produce a spastic uterus with increase in frequency and height of contractions as the tonus diminishes due to passing off of the maximal reactions.

Morphine is capable of significantly reducing the motility and tone of the postpartum uterus, and our observations suggest caution in postpartum medication for pain due to the possibility of uterine relaxation and increased postpartum hemorrhage.

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10515 CARNEGIE AVENUE

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**Marenzi, A. D., and Gerschman, R.**: Phosphorus of the Plasma and Blood During Ether Anesthesia, Rev. Soc. argent. de biol. 10: 64, 1934.

The authors studied the different fractions of phosphorus of the blood before, during and after ether anesthesia. They conclude that the increase of inorganic phosphorus does not come from the hydrolysis of the several compounds of phosphorus in the blood, but is due to the liberation of phosphorus by muscle tissue during anesthesia.

MARIO A. CASTALLO.

**Reich, A.**: Leucorrhoea, Am. J. Surg. 25: 398, 1934.

The following treatment has been found to be effective in gonorrheal cervicitis and infection by trichomonas vaginalis as well as in the nonspecific infection. The vaginal speculum is introduced and the vagina is dried out. A tablespoon of granulated sugar is put on a small piece of paper, with a tablespoon of ointment of salicylic acid, grains 10; mercuric ointment drachm 2, and zinc ointment up to 1 ounce. Rolled up together in the paper, they are introduced into the vagina followed by a tampon, which is removed in twenty-four hours. No douche is necessary. The sugar and ointment produce a syrupy mixture which is highly bactericidal and remains effective for about one week. At the end of this time a new treatment is given.

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## HARMFUL EFFECTS OF CERTAIN CHEMICAL SUBSTANCES UPON THE UTERUS OF THE RAT

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THE introduction of chemical substances into the uterine cavity for the purpose of interrupting pregnancy is a practice by no means recent, tincture of iodine having been used for this purpose for half a century. Since about 1930, however, the introduction of various types of irritant pastes (Interruptin and Provocal) has awakened renewed interest in this method of inducing abortion, and apparently the use of these preparations is becoming more and more widespread.

Very little experimental work has been published concerning the action of abortifacients in animals, probably because their widespread use in the human being is comparatively recent and reasonably satisfactory, and also because it seemed unlikely that any knowledge having clinical value could be acquired by such a study. This in view of the great differences in the anatomy and physiology of the human uterus as compared with the uteri of laboratory animals and also in view of the difference in the types of placentation. We fully subscribe to the dictum that in this field, above all others, it is extremely hazardous to apply conclusions reached from the study of one species of animal to the human being, and are not at all certain that anything of clinical importance has been learned in this study. On the other hand, it would seem that where a given agent produces deleterious effects in an animal as hardy as the rat, with its high degree of resistance to infection and relative indifference to trauma, he need not be considered an alarmist who advises caution in the use of similar agents in the human being.

This study, which can only be considered preliminary in scope, had for its object to determine:

1. Which of the substances present in the commonly used pastes was the effective abortifacient.
2. Whether abortion might be induced by other agents.
3. What the after-effects of the abortifacient upon the uterus might be.

*Experimental.*—In some respects, the rat is an ideal animal for a study of this sort. The uterus is bicornate, with a septum dividing the cervical canal, and it is therefore possible to introduce the agent being studied into one horn, leaving the other horn uninjected as control. Our method was as follows: Rats were smeared, and, when in estrus, placed with

males and breeding observed. When the desired stage of pregnancy had been reached (seven days was used in most instances as at this time the fetuses are visible, although still very small), they were placed under ether anesthesia, a short midline incision from the clitoris headward was made and the uterus examined. A small glass cannula was passed through the cervical canal into one horn, and the material being studied, warmed to body temperature, introduced from a hypodermic

TABLE I. EFFECTIVENESS OF VARIOUS CHEMICAL SUBSTANCES APPLIED TO 252 RATS

Positive: All fetuses in injected horn killed.

Negative: At least one living fetus in injected horn on seventeenth day.

MATERIAL INJECTED (DILUTION)	NUMBER OF ANIMALS	DAY OF INJEC- TION	RESULTS OF INJECTION		APPEARANCE OF UTERUS ON SEVENTEENTH DAY OF GESTATION
			POS.	NEG.	
1. Physiologic saline:					
a.	9	4	6	3	Normal in all cases
b.	26	7	2	24	Normal in all cases
2. Isotonic potassium iodide	9	7	0	9	Normal in all cases
3. Leunbach paste:					
a. Straight	12	7	12	0	Injected horn thin and brown; several with cheesy masses
b. Dil. 2:5	19	7	15	4*	Fair condition, but with walls thin and pale
c. Dil. 1:5	13	7	10	3	As in preceding group
4. Iodine solution:					
a. 1.0 per cent Con.	13	7	12	1*	Practically normal
b. 2.5 per cent Con.	8	7	8	0	Practically normal
5. Potassium oleate					
a. Straight	6	7	6	0	Poor condition, walls thin and pale
b. Straight	8	14	6	2	Examined on twentieth day. Resorption slow
c. Dil. 1:5	4	7	4	0	Fair condition
d. Dil. 1:10	14	7	14	0	Fair condition
e. Dil. 1:10	7	14	7	0	Examined on twentieth day. Resorption more rapid than in "b"
f. Dil. 1:20	7	7	3	4	Good condition
6. Buffer solution					
a. pH 11.29	6	7	2	4	Normal
b. pH 12.06	13	7	8	5	Normal
c. pH 14.0	11	7	11	0	Uteri thin and yellow, masses of cheesy material
7. Corn oil					
a.	13	7	10	3	Resorption slow, condition of uteri fair
b.	9	14	0	9	Apparently no effect when injected so late
8. Hexylresorcinol					
a. Dil. 1:10,000	6	7	2	4	Normal
b. Dil. 1:1,000	7	7	6	1	Normal
9. Hypertonic NaCl					
a. Con. 5 per cent	9	7	2	7	Normal
b. Con. 10 per cent	10	7	4	6	Normal
10. Unmedicated tragacanth jelly	13	7	8	5	Normal

\*One living fetus, usually at ovarian end of horn.

syringe attached to the cannula. The amount introduced varied with the size of the uterus, usually 0.1 to 0.2 c.c. comfortably filled the horn, undue distention being avoided. The incision was closed and the animal returned to her cage. On the seventeenth day the animal was again opened under ether and the effect noted. The animal was then permitted to produce and nurse her litter, after which she was given a rest period of from two to three months. She was then bred again, and toward the end of this second gestation period was sacrificed. The appearance and fertility of the horn which had been injected from three to four months previously was noted. Physiologic saline and isotonic potassium iodide solutions were used as controls to make sure that neither the operation itself nor the mere introduction of material into the uterus would cause abortion. The findings from a total of 252 rats are reported in this paper.

*Results.*—The results obtained are shown in Tables I and II.

TABLE II. RESULTS OF REBREEDING RATS THREE TO FOUR MONTHS AFTER INJECTION OF ABORTIFACIENT CHEMICALS

MATERIAL INJECTED	NUMBER OF RATS REBRED	RESULTS
1. Physiologic saline	22	21 pregnant in injected horn; appearance of all cases normal
2. Isotonic potassium iodide	9	6 pregnant in injected horn; all normal in appearance
3. Leunbach paste		
a. Straight	8	None pregnant in injected horn; all in very bad shape
b. Dilute	14	One pregnant in injected horn; two others looked all right. Other eleven in poor shape, uteri very thin, threadlike; others with large green masses
4. Iodine solution		
a. Con. 1 per cent	11	Seven appeared normal, three being pregnant. Other four very bad, masses of necrotic material representing fetuses of second crop undergoing resorption
b. Con. 2½ per cent	7	None pregnant; much like last four in preceding group
5. Potassium oleate		
d. Dil. 1:10	11	Three pregnant in injected horn; other eight like Leunbach-injected animals
6. Buffer solutions		
b. pH 12.06	9	Seven pregnant in injected horn; others look normal
c. pH 14.0	8	None pregnant. In very bad shape. Resemble Leunbach animals
7. Corn oil	7	Five pregnant; others normal
8. Hexylresorcinol		
b. Dil. 1:1,000	5	None pregnant but look normal
9. Hypertonic NaCl		
a. Con. 5 per cent	7	Five pregnant; others normal
b. Con. 10 per cent	7	Five pregnant; others normal
10. Unmedicated traganth jelly	9	Seven pregnant; others normal



*Comment.*—As far as the control material is concerned, the introduction of physiologic saline killed the fetuses in six out of nine animals if injection was made on the fourth day. The fetuses were probably not firmly implanted at this time and were washed out. This suggests the early injection of inert material as a possible preventive for pregnancy and this point demands further investigation. In two cases, out of the other 35 controls injected on the seventh day (26 with physiologic saline and 9 with isotonic potassium iodide), the fetuses were killed. We believe this was due to some extraneous factor and is not significant.

The material to which we gave the greatest consideration was Leunbach paste (sold abroad as "Provocal"), since this is the paste most widely used in this country. The *Journal of the American Medical Association* 98: 2155, 1932) contains a report of the Bureau of Investigation concerning this substance. Apparently results abroad are not entirely favorable; the Bureau finding reports of some 25 fatal accidents resulting from its use. In the hands of some obstetricians no untoward results have been noted, while in some clinics, on the other hand, the use of any preparation of this type is prohibited. The formula is given in the article mentioned; it contains soap, iodine, potassium iodide, tincture of benzoin, tincture of myrrh and thymol. "Interruptin," introduced by the German pharmacist Heiser, is apparently a secret preparation, but from the article by H. Wolf (*Monatschr. f. Geburtsh. u. Gynäk.* 88: 442, 1931), is similar in its essential components to Leunbach paste.

We used Leunbach paste in three concentrations, straight, diluted 2 parts of paste to 5 parts water and one part paste to 5 parts water. In its original strength it gave positive results in all of 12 animals; diluted, it was not invariably effective, although the few fetuses left alive were usually well up in the ovarian end of the horn and might not have been reached by the paste. The uteri, upon examination on the seventeenth day of gestation did not look healthy, in many there were masses of greenish, cheesy material while in others the horn looked pale, somewhat yellowish and thin. This effect was much more marked at the end of the four-month rest period when the animals were examined after having been bred the second time. Not one of eight given straight Leunbach paste became pregnant on second breeding and only one of 14 given diluted paste became pregnant. In many of these animals the horn which had been injected several months previously was so small it could hardly be found, histologic examination in several cases showed the epithelium completely gone and the lumen grown together with connective tissue. It is our opinion that many of these uteri could never again have become pregnant, so complete was their destruction. In other cases, where the uterus had apparently not been so badly damaged, nidation had occurred followed by some degree of fetal development, but the fetuses had then died and were undergoing resorption. It should also

be mentioned that 6 of the 44 animals given Leunbach paste died within one month's time; these were the only rats out of nearly 300 that died as a result of the injections. These animals seemed to be suffering from a generalized infection of the entire abdominal cavity, huge greenish abscesses formed, the animals lost weight rapidly and died. The cause of death in the human cases reported in the literature was presumed to be air or soap embolism. We purposely injected air along with soap into several animals and also injected one series with corn oil; no death resulted.

We next attempted to learn which of the constituents of the paste was the active ingredient. Since the base used is soap it seemed advisable to begin with this agent. Neutral potassium oleate was prepared and injected in varying dilutions. When injected on the seventh day, dilutions as great as one part soap in ten of solution gave invariably positive results in a total of 24 animals; in a dilution of 1 to 20, however, the results were not certain. The appearance of these uteri on second breeding after several months rest did not differ greatly from those receiving Leunbach paste, but a higher percentage, three out of eleven, became pregnant the second time.

The next constituent investigated was the iodine. This was used in a 1 per cent solution and in a  $2\frac{1}{2}$  per cent solution, dissolved in isotonic potassium iodide. The former was positive in twelve out of thirteen animals and the latter in all of eight. These uteri looked nearly normal when examined the first time, but again, the second breeding attempt showed that serious injury had been suffered, particularly by the group receiving the stronger solution. None of seven animals remained pregnant in the injected horn, several of these horns were enormously distended with a black fluid, while others were filled with cheesy material representing the resorbing fetuses of the second pregnancy. In none of these animals, however, was there the actual destruction of tissue and atrophy of the horn as a whole which resulted from Leunbach paste injection. It is quite possible, we believe, that the horn might have recovered, in time.

It would seem, therefore, that either the soap or the iodine, present in Leunbach paste, would cause abortion. The other ingredients were not investigated.

In studying the possibility of other agents which might have an abortifacient action without the effect of sterilizing the uterus, the first substance that suggested itself was a buffer solution having a fairly high pH, on the assumption that the action of the soap was due to its alkalinity. Solutions having a pH of 11.29, 12.06, and 14 (a tenth-normal solution of sodium hydroxide) were used. Of these, only the latter was reliably abortifacient, but again, its use resulted in horns that were decidedly abnormal after three months' time. Of eight animals rebred,

none carried the fetuses in the injected horn through, although in several cases implantation and some growth of the fetuses had occurred, prior to death and resorption. It appeared as though the resorption of these dead fetuses was hindered by the low degree of vascularity prevailing in the horn; they appeared mummified, but covered with an outer layer of greenish necrotic material. These uteri, on the whole, resembled those of the Leunbach paste-injected animals.

Several shots in the dark were taken in the hope of accidentally stumbling upon some effective agent. Thus, corn oil was used in the hope that it might have a loosening effect upon the placenta; hypertonic saline, in 5 per cent and 10 per cent concentrations, in the hope that it might kill by dehydration; hexyresoreinol and unmedicated gum tragacanth. As will be noted from the tables, none of these agents was reliable. It should be noted that, where positive results were obtained, rebreeding and later examination showed a uterine horn normal in appearance, even though not invariably pregnant.

*Discussion.*—The most significant finding in this investigation appears to be the long-continued action of the effective abortifacients upon the uterus and the sterility and pathologic state resulting therefrom. As has been stated, it is a question how much of what has been found to occur in the rat would occur in the human being. The rat, for instance, does not abort readily, the fetuses die and are resorbed; in the human being, abortion would tend to eject the agent causing the abortion. Menstruation in the human being would tend periodically to flush out the offending substance. Other essential differences suggest themselves. If, however, there should be any similarity of action and result, it is obvious that an abortion accomplished by the use of such agents as Leunbach paste would be an extremely dangerous proceeding. Even though it only rendered the uterus sterile for a few years, that might mean an extremely unhappy state of affairs for the woman for whom an abortion today may be advisable but with a change in the state of health or finances, a pregnancy next year might be greatly desired. It would at least seem to be the part of wisdom to proceed with caution until a sufficient study of the question of ensuing pregnancies following an abortion by means of these agents has been made. In the meantime further laboratory study of abortifacients upon laboratory animals might well be undertaken, particularly upon primates, or at least upon animals which abort more readily than does the rat.

Thorough histologic study of the uteri and fetuses during the period following the introduction of the abortifacient might also be valuable in indicating its mode of action, whether by killing the fetus directly or by affecting either the uterus or placenta. Such a study might give an indication as to what type of chemical substance could be expected to have an abortifacient action without the deleterious effects described and make a thorough study of such substances less laborious and more

likely to be successful. Also, as has been pointed out, the time factor should be thoroughly studied, as possibly a milder agent might be effective in the pre-implantation stage. The discovery of such an agent or technic might have value as a follow-up measure in the prevention of conception in cases where, for any reason, the efficacy of the contraceptive used was doubtful.

#### SUMMARY

1. The effective agent in Leunbach paste may be either the soap or the iodine, either substance alone being an effective abortifacient.

2. In the rat, every agent that is dependably abortifacient will, in most cases, render the injected horn sterile for at least a three months' period and will also cause varying degrees of pathologic abnormality.

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### HEMORRHAGIC ENCEPHALITIS (NEOARSPHENAMINE) IN OBSTETRIC PATIENTS

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THREE obstetric patients, who died early in the course of anti-syphilitic therapy, have been observed during the past five years. In each instance, the clinical picture was that of hemorrhagic encephalitis, and in two this diagnosis was supported by the anatomic findings at autopsy. Two patients were pregnant near term and one had recently been delivered, so that the appearance of generalized convulsions, followed by coma in the last two, aroused a suspicion of eclampsia. These similarities to the convulsive toxemia of late pregnancy provided interesting problems of differential diagnosis and prompted the following detailed reports of the clinical developments and, in two instances, of the anatomical findings.

CASE 1.—K. R. (Hospital No. D 4452), aged nineteen years, was admitted July 8, 1929, in the eighth lunar month of her first pregnancy. A strongly positive blood Wassermann reaction had been detected by the home physician shortly before admission. On July 12, the Wassermann and Kahn reactions were again reported strongly positive. The date of the initial infection could not be determined.

The family and past histories were not significant.

General physical examination was negative, the pregnancy was progressing normally and corresponded to the menstrual history. There was no edema, the urine was free from albumin, and the blood pressure was 100/55 mm.

Antisyphilitic treatment was instituted two days after admission, and consisted of: July 10, 2 min. of gray oil, intramuscularly; July 11, 0.2 gm. neoarsphenamine,

intravenously; July 15, 0.4 gm. neoarsphenamine, intravenously; July 17, 2 min. of gray oil, intramuscularly; July 18, 0.4 gm. neoarsphenamine, intravenously; July 22, 0.4 gm. neoarsphenamine, intravenously; July 24, 2 min. of gray oil, intramuscularly; July 25, 0.4 gm. neoarsphenamine, intravenously; July 29, 0.4 gm. neoarsphenamine, intravenously; July 31, 2 min. of gray oil, intramuscularly.

There had been no reaction to the medication except that on July 30 and 31 there was slight headache which did not demand treatment. Weekly examinations had shown the urine to be free from albumin and casts, and the systolic blood pressure had never been higher than 120 mm.

Early in the morning of August 1 (three days after the sixth, and twenty days after the first neoarsphenamine injection), the patient vomited and passed rapidly into a state of spastic paralysis which prevented speech. Responding to direct questions, she indicated that she had a severe headache and that she could not move the arms, which were drawn tightly to the body and were flexed at the elbows with marked pronation of the thumbs. The legs were extended and rigid though the right leg was more spastic than the left. The muscle reflexes were abolished except for the radials which were normal. Chvostek's sign was negative. Sensation was markedly impaired, pain being appreciated only over the chest. The blood pressure was 120/70, and the heart sounds were clear. The temperature was 98.7° and the pulse 86 per minute. The pupils responded poorly to light, but the ocular fundi were normal. The total leucocyte count was 14,300. A catheterized specimen of urine showed no abnormality. Two grains of phenobarbital were given by mouth.

Later on the same day, the spinal fluid, which was under normal pressure, showed 3 cells per c.mm., with no demonstrable globulin or blood: the total protein was 76 and the sugar 135 mg. per 100 c.c. Blood chemistry revealed: Urea nitrogen 10.8, creatinine 1.0, and uric acid 5.0 mg. per 100 c.c. Both the direct and indirect van den Bergh reactions were negative.

Gastric lavage gave little result. One-fourth grain of morphine and 30 gr. of chloral were administered, and tap water was given by rectum.

The patient's condition became rapidly worse during the day. The spasticity gave way to flaccidity, the temperature rose to 104° F., and coma developed. The radial periosteal reflexes remained undisturbed but the knee jerks, biceps and abdominal reflexes could not be elicited, and plantar stimulation provoked flexion. No convulsions were observed. Respiration became irregular and labored, and the temperature rose to 106° (rectal). Death occurred at 3:30 A.M., August 2, respirations stopping a few minutes before the heart. Delivery had not been effected.

Complete postmortem examination was begun six hours after death. The pathologic diagnoses were: moderate congestion of the lungs; marked degeneration of the renal tubules; acute encephalitis, toxic, arsenical.

Throughout the brain there was marked involvement of the capillaries, which were practically plugged with fibrinous thrombi, containing many leucocytes. The fibrin, which was adherent to the vessel walls, formed in some places a loose reticulum and in others a solid hyalinized plug. In certain areas, the endothelium of the vessel walls was edematous and showed proliferation and desquamation into the lumina. Polymorphonuclear leucocytes were seen invading the vessel walls and infiltrating the surrounding tissues. The Virchow-Robin space contained a delicate fibrinous exudate.

Small recent punctate hemorrhages were present in several areas. The blood was largely in the perivascular spaces and in the surrounding brain tissue. Edema was marked, especially in the white matter of the internal capsule and the corpus callosum. The perivascular spaces were widely dilated, the supporting tissues of the white matter were thinned out, and numerous small cystic areas were present, some of which had coalesced. The cerebral lesions evidently represented an acute, toxic

encephalitis, probably due to arsenical poisoning. The damage was apparently very recent so that there had been insufficient time for striking morphologic changes.

CASE 2.—I. B. (Hospital No. F 8877), aged twenty-two years, was admitted Oct. 19, 1931, in the eighth month of her first pregnancy. On admission, the urine was normal, the blood pressure 120/80, and general physical examination revealed no gross abnormalities. On October 26, smears from the urethra and cervix showed gonococci, and local treatment was instituted. On October 19, and again on October 21, the blood Wassermann reaction was reported strongly positive to both alcoholized and cholesterinized antigens, and the Kahn test was likewise strongly positive. There were no clinical signs of syphilis, but the spinal fluid Wassermann was positive. The hemoglobin was 90 per cent, and the total leucocyte count was 9,300. The patient was treated as follows: October 27, 0.2 gm. neoarsphenamine, intravenously; October 30, 0.4 gm. neoarsphenamine, intravenously; November 2, 0.4 gm. neoarsphenamine, intravenously.

Following the first two injections there was considerable pain and tenderness in the arms around the injection sites, probably due to extravasation of the solution into the subcutaneous tissues, but no evidence of any general reaction.

On November 3, the day after the third injection (six days after institution of treatment), the patient was severely nauseated and complained of abdominal pain. Headache, backache, and dizziness appeared on the next day, November 4. Intermittent abdominal pains continued, and early in the morning of November 5, the cervix was found by rectal examination to be 2 to 3 cm. dilated. In view of the small size of the fetus,  $\frac{1}{4}$  gr. of morphine was given. When the hypodermic injection was made, the patient screamed and immediately developed a generalized convulsion, during which she scratched her face and bit her lips. Urine obtained by catheter contained no albumin or abnormal cellular elements. There was no edema. After the convulsion, the patient was disoriented and stuporous. The deep reflexes which had been slightly hyperactive became markedly diminished. There was no rigidity of the neck and no skin eruption. The temperature rose from normal to 102° F. A second generalized convulsion occurred at 4:00 A.M.

During the late morning of November 5, almost continuous twitching appeared together with a rapid succession of convulsions, five in all, which varied markedly in extent. The first of this series was generalized, the second almost entirely confined to the right side, while the third involved only the left side. The blood pressure shortly after a convulsion was 105/50. The ocular fundi were essentially normal. After this series of convulsions the patient became comatose and had one more generalized convulsion before she died, undelivered, at 9:30 P.M. Treatment consisted of intravenous injections of sodium thiosulphate and of glucose solution. Autopsy was not permitted.

It was felt that the patient probably died from hemorrhagic encephalitis resulting from the intravenous arsenical treatments which she received because the clinical picture was so similar, except for the convulsions, to that observed in the first case, where the diagnosis had been confirmed by postmortem findings. The absence of edema and of hypertension together with the nature of the convulsions was entirely unlike eclampsia. We have never seen an eclamptic convulsion which was other than generalized, and doubt whether unilateral seizures ever appear in this disease.

CASE 3.—A. J. T. (Hospital No. H 12,970), aged twenty-two years, a secundigravida, was admitted on Nov. 27, 1933, in the tenth lunar month of a normal pregnancy. The previous pregnancy had terminated in December, 1932, as a spontaneous miscarriage at fourteen weeks. Blood Wassermann reactions on November 28 and on November 30 were strongly positive (+++), as was the Kahn test. The spinal

fluid Wassermann reaction was positive (+++++) on November 28. Urine passed on the same day was normal, and the blood pressure was 112/88. Antisyphilitic treatment was given as follows: December 1, 0.2 gm. neoarsphenamine, intravenously; December 4, 0.4 gm. neoarsphenamine, intravenously, 2 min. of gray oil intramuscularly; December 7, 0.4 gm. neoarsphenamine, intravenously.

The patient was delivered spontaneously on December 8, at 12:43 A.M., after a labor lasting one hour and thirty-eight minutes. The child, which weighed 3,193 gm. at birth, appeared grossly normal. The Wassermann reaction on the cord blood was strongly positive (+++++), but the Kahn test was negative. Roentgen ray films of the long bones revealed no evidence of congenital syphilis. The child was discharged on December 21, 127 gm. above birth weight.

Within a few hours of delivery, the patient's temperature rose to 100.6° F., but returned to normal within twelve hours (delivery reaction?). On December 9, there were no complaints except for a few after-pains. The following day the patient complained of a feeling of general malaise and responded slowly to questions. The pulse was 128, the temperature 100° F., and the blood pressure 145/105. The urine showed a moderate trace of albumin with numerous finely granular casts and many pus cells, and occasional red blood cells. One hundred and fifty cubic centimeters of 50 per cent glucose solution were given intravenously.

Throughout the afternoon she remained sluggish and became progressively less reactive. At 4:00 P.M., unconsciousness supervened, and at 4:50 P.M. there was a generalized convulsion followed by marked cyanosis with definite respiratory difficulty. Three more generalized convulsions followed in rapid succession before the patient was brought under the influence of  $\frac{1}{4}$  gr. of morphine sulphate, and  $7\frac{1}{2}$  gr. of sodium amytal. Lumbar puncture showed the spinal fluid under normal pressure, but the Pandy reaction was two-plus, and there were 20 lymphocytes per cubic millimeter. The blood pressure had risen to 160/110 mm. Blood chemistry revealed: uric acid, 5.6; urea nitrogen, 11.9; and creatinine, 1.6 mg. per 100 c.c., while the CO<sub>2</sub> combining power was 49.1 vol. per cent, and the van den Bergh was 0.1. The biceps, triceps, knee-jerks, and tendon achilles reflexes were hyperactive, but the abdominal reflex was absent. Plantar stimulation provoked flexion with slight extension of the great toes. Bilateral ankle clonus was present. Because of the respiratory difficulty, oxygen was administered by nasal tube.

At 8:55 P.M.  $\frac{1}{60}$  gr. of atropine sulphate was given to combat excessive mucous secretion in the upper respiratory tract. It was noted that the neck was moderately stiff. Urine obtained by catheter at 9:15 P.M. showed a moderate trace of albumin, many finely and coarsely granular casts, and occasional red and white blood cells. The blood pressure was 120/75 mm., respirations were 24 and the pulse 100 per minute. Twenty grains of chloral hydrate and 40 gr. of sodium bromide were given by rectum.

On December 10, at 12:30 A.M., the temperature was 105° F. (axillary), the pulse 140 to 160 per minute, and the blood pressure 120/40. Death occurred at 1:35 A.M., the heart stopping one minute after respirations had ceased. The axillary temperature shortly before death was 107° F.

Clinical diagnoses included: (1) A vascular type of neurosyphilis, (2) hemorrhagic encephalitis, and (3) postpartum eclampsia. The picture so closely resembled that of the previous proved case of hemorrhagic (arsenical) encephalitis (Case 1) in (1) the time of onset in relation to the last injection of neoarsphenamine, (2) the clinical determination of marked central nervous system disturbances, and (3) the rapidly fatal outcome, that this seemed the most probable diagnosis. There had been, however, none of the usual prodromes, such as nausea and vomiting, headache, or dizziness. Eclampsia was suggested by the presence of a slight hypertension and the determination of a moderate albuminuria and cylindruria, even in

the absence of edema, but the late appearance of the first convulsion (thirty-nine hours after delivery) and the absence of earlier evidence of a toxemia of late pregnancy argued against this diagnosis.

Necropsy was performed seven hours postmortem. The final pathologic diagnoses included: bronchopneumonia, postpartum uterus, syphilitic aortitis, chronic syphilitic leptomeningitis, and hemorrhagic (arsenical) encephalitis.

The brain appeared normal grossly and the convolutions were well defined. The cerebral vessels were injected, but the walls were thin and the lumina were not occluded. The meninges were normal and showed no localized thickening.

Microscopically, there was considerable congestion of the meningeal vessels but no hemorrhages in the cerebrum. In certain areas, especially over the cord, the meninges were thickened and infiltrated with chronic inflammatory cells, chiefly lymphocytes and plasma cells. Edema of the brain tissue was questionable. Some of the cerebral vessels, more especially those in the basal ganglia, showed perivascular infiltration with leucocytes. A few very small hemorrhages were present, for the most part in the basal ganglia, where certain small vessels contained polymorphonuclear leucocytes, some of which appeared to be within the vessel wall rather than perivascular. This was interpreted as evidence of an arteritis.

The typical history for an arsenical reaction and the finding of minute hemorrhages in association with a definite arteritis, although the presence of edema was doubtful, seemed to justify the diagnosis of arsenical encephalitis. The inability to detect arsenic chemically in the blood or brain tissue may be explained by a fixation of the metal in tissues other than the brain after its removal from the blood stream.

#### SUMMARY

Three young women, aged respectively nineteen, twenty-two, and twenty-two years, died during late pregnancy or shortly after delivery, in the course of antisyphilitic therapy directed at latent syphilis detected by routine blood Wassermann tests. In two instances, hemorrhagic encephalitis was demonstrated postmortem, while in the third the clinical picture made the diagnosis reasonably certain. Neoarsphenamine was employed in each case; six injections totaling 2.2 gm. in Case 1, and three injections totaling 1.0 gm. in each of the other two. In addition, four injections of gray oil (two minims each) were given to the first patient and one similar dose to the third patient.

In each instance the initial dose was within the limit usually recommended and succeeding doses were not large, being smaller than the maximum dose (0.45 gram) recommended by the Council of the German Public Health Service,<sup>1</sup> but somewhat larger than the maximum recommended by Klaften<sup>2</sup> for use in pregnant women. Moreover, injections were made twice weekly, instead of once each week as is commonly advised. It should also be noted that in two instances the spinal fluid Wassermann reaction was positive despite absence of clinical evidence of cerebrospinal syphilis. There is no good reason to believe that such patients are especially liable to the appearance of encephalitis.

In each instance, cerebral symptoms of arsenical poisoning developed within seventy-two hours after the final injection of neoarsphenamine, and death occurred within three days of the initial manifestations, or



on the third to the fifth day after the last injection. Two patients developed convulsive seizures, which naturally suggested puerperal eclampsia, a condition which must obviously be considered whenever convulsions appear in the latter semester of pregnancy or shortly after delivery. In Case 2, the bizarre character of the convulsions, and, in Case 3, the anatomical findings clearly removed this possibility.

#### DISCUSSION

These three fatalities in a relatively small series of syphilitic pregnant women under treatment with presumably the safest of the modern arsenicals naturally raises the question of increased susceptibility to the toxic effects of arsenic during gestation. Nowhere can we find this subject discussed with any thoroughness, and it has seemed advisable to review briefly the available literature.

Cole and his collaborators<sup>3</sup> are of the opinion that young adults generally are more susceptible to the toxic effects of arsenical injections, and that women are more susceptible than men, an opinion which is also shared by Klaften,<sup>2</sup> Pritzi,<sup>4</sup> and Ireland.<sup>5</sup> The danger seems likewise to be greater early in the course of treatment (Ireland,<sup>5</sup> Cole et al.,<sup>3</sup> and Phelps and Washburne<sup>6</sup>) with symptoms more commonly appearing after one to four injections. Cole's<sup>3</sup> statistics indicate that those with latent syphilis are more likely to develop reactions than are those with early lesions, and the common finding in pregnant women is a latent infection, which is discovered only by routine serologic tests.

Klaften,<sup>2</sup> Pritzi,<sup>4</sup> McKelvey and Turner,<sup>7</sup> and Clason<sup>8</sup> apparently believe that pregnancy increases the danger of serious reactions, while the first-named<sup>2</sup> attributes a pernicious influence to menstruation and recommends a reduced dosage during these two physiologic states. Gammeltoft<sup>9</sup> quotes Kristjansen as saying that among all patients treated with salvarsan at Rudolph Bergh's Venereological Hospital during a ten-year period four or five died from salvarsan poisoning, and three were pregnant women. Klaften<sup>2</sup> quotes Meirowsky as having collected data on twenty-three salvarsan fatalities among women, fourteen of whom were pregnant. This author likewise states that he has observed women who showed salvarsan reactions while pregnant, but who after delivery were given the same drug without observable bad effects. In the past five years there have been eight deaths at the University Hospitals from hemorrhagic (arsenical) encephalitis; all of the patients were females and of these three were pregnant. On the other hand, McCord<sup>10</sup> says: "With an experience of many thousands of doses of all kinds of arsenical preparations given to pregnant women, I have never seen a reaction that approached a fatality: I rarely see a reaction of any kind." The fortunate experience of this observer may be attributed to the fact that his patients are all colored women, who, according to certain investigators, Cole et al.,<sup>3</sup> are more immune to the common toxic effects than are white women.

Pritzi<sup>4</sup> believes that the danger of toxic reactions increases as term is approached, and that the increased susceptibility is due to changes in the body colloids and lipoids, which are well known to develop during gestation. Eastman<sup>11</sup> has, however, pointed out that the placenta acts as a storage center for injected arsenic, which is then gradually set free in the blood for long periods after the injection, and it is possible that this factor is significant, since it involves a more or less continuous introduction of arsenic into the system. This phenomenon is utilized to explain the relatively greater therapeutic efficiency of small doses of the arsenicals given to

pregnant women, and may also bear some relation to their apparently greater susceptibility to its pernicious effects. It must also be remembered that pregnancy presumably produces a certain amount of capillary alteration and that the lesions of arsenical encephalitis are, according to Ireland<sup>5</sup> "doubtless produced by capillary vascular injury or thrombosis." Scott and Moore<sup>12</sup> have suggested that the destructive and dilating action of arsphenamine on the blood vessels is not counteracted by epinephrine, which is deficient because of the arsenical destruction of the suprarenals, an opinion which is concurred in by Brittingham and Phinizy.<sup>13</sup> They also believe that "the delayed arsphenamine reaction is nothing more than an arsenic poisoning due to the liberation of poisonous trivalent arsenic from the faultily eliminated arsphenamine."

There is considerable difference of opinion concerning the possible bad effects of the modern arsenicals upon pregnancy. Gammeltoft<sup>14</sup> believes that the salvarsan series of drugs does not cause abortion, but quotes Gougerot, Merklen, Wolf, and Neel as expressing an opposite opinion. Klasten<sup>2</sup> doubts a cause-and-effect relationship, although he has seen abortion follow administration of the arsenicals, while McKelvey and Turner<sup>7</sup> insist that arsphenamine does not increase the incidence of abortion and is without deleterious effects upon the fetus.

The Council of the German Public Health Service,<sup>1</sup> in setting up criteria for the use of arsphenamine preparations recommends especial care in certain organic diseases and in pregnancy and advises initial trial doses, with full doses only if the drug is well borne. Klasten<sup>2</sup> and Pritzi<sup>4</sup> recommend that the maximum dose of neoarsphenamine for pregnant women be 0.3 gm., with proportionate maxima for the other arsenicals. Stokes et al.,<sup>15</sup> in outlining a "standard treatment procedure in early syphilis," likewise recognize the need for care in the treatment of pregnant women if reactions are to be avoided.

It is well recognized that, even under ideal conditions and with every precaution satisfied, reactions will follow the intravenous use of antisyphilitic arsenicals. Excluding early febrile sequelae, such as "endotoxic reactions" due to the liberation of the "syphilitic toxin" from the spirochetes by the destructive action of the drug, and the "water fever" due to pyrogenic factors in the water used for solution of the drug, Parnell and Fildes<sup>16</sup> found that among 6,588 injections of neoarsphenamine given to 1,250 patients there were 78 reactions, slightly over 1 per cent. The greatest danger was during the first series and after the second, third or fourth doses, and particularly after the third, when almost one-half of the reactions occurred. Cole et al.<sup>3</sup> in "very close to 78,350 injections" of the various arsenicals found that 15.3 per cent of the 1,212 patients studied showed one or more arsenical complications of treatment (19 per cent of the latent and 14.3 per cent of the early cases). There were twelve fatal cases: "six from hemorrhagic encephalitis, five from crustaceous dermatitis exfoliativa, and one from acute severe arsenical hepatitis, all cases treated less than six months." Eight of the twelve fatal cases had received no more than four injections. Ireland<sup>5</sup> noted reactions in 15 per cent of the female and 8 per cent of the male patients in his series of 2,100 cases, but seemingly had no fatalities. Klasten<sup>2</sup> quotes figures to show that fatal reactions occur in from 1 in 20,000 to 1 in 30,000 injections of neoarsphenamine, provided the maximum dosage is not more than 0.6 gm. Phelps and Washburn<sup>6</sup> reviewing 272,354 injections recorded one death in 16,021 injections in their entire series, with the ratio 1 in 22,625 for arsphenamine and 1 in 14,844 for neoarsphenamine.

The more dangerous of the late reactions are exfoliative dermatitis, stomatitis, acute yellow atrophy of the liver (jaundice), and hemorrhagic encephalitis<sup>17</sup> with the last responsible for at least one-half of all deaths.<sup>18</sup> Phelps and Washburn<sup>6</sup> record one fatality from hemorrhagic encephalitis for every 1,171 patients treated,

or one for every 23,000 injections. These investigators record twenty deaths from this complication, with ten occurring after the second injection, as against four deaths from dermatitis and none from acute yellow atrophy of the liver.

The symptomatology of arsenical hemorrhagic encephalitis varies considerably, but there is usually early evidence of involvement of the central nervous system, with tonic and clonic convulsions and coma predominating. The convulsive seizures may be generalized or unilateral and are commonly followed by coma which terminates in death. More rarely there may be delirium with fever, vomiting, and shock. Prodromes, in the form of nausea and vomiting, headache, restlessness, and fever are frequently observed, but their serious significance is not appreciated until other symptoms supervene. In a recent case of exfoliative dermatitis developing shortly after delivery, the prodromes aroused a strong suspicion of early encephalitis, but on the following morning the development of a typical skin rash was associated with rapid disappearance of the mild nervous phenomena. Other symptoms and signs, as enumerated by Phelps and Washburn<sup>6</sup> include: prostration, tachycardia, nervousness, congestion of the throat and eyes, backache, severe abdominal pain, diarrhea, swelling of the posterior cervical glands, delirium, cyanosis, and slight muscular twitchings. In some instances, there may also be a paralysis of certain muscle groups, of a flaccid, or spastic character.

In pregnant and recently delivered women, the appearance of convulsions and coma naturally arouses a suspicion of eclampsia. However, the usually atypical character of the convulsions, the absence of hypertension and albuminuria, and the history of intravenous arsenical injections within a few days should suggest hemorrhagic encephalitis. Moreover, signs of serious central nervous system involvement quickly appear; the deep reflexes are at first hyperactive but soon become greatly diminished or absent, Babinski's sign may be positive, squint may appear, disturbances of sensation may be detected, disorientation may be observed, and ankle clonus may be elicited. Final diagnosis in doubtful cases may rest upon the postmortem demonstration of edema and small hemorrhages in the brain and spinal cord, as well as in the skin, pericardium, and various viscera. Hemorrhages into the central nervous system alone are pathognomonic; they usually appear as small punctate extravasations of blood around the capillaries, but occasionally the coalescence of several such small hemorrhages produces a larger hemorrhagic area. Hyaline thrombosis of the capillaries is also frequently observed.

Death usually occurs within ninety-six hours, but Dickens,<sup>19</sup> Phelps and Washburn,<sup>6</sup> and Klawns<sup>2</sup> have reported patients with symptoms suggesting hemorrhagic encephalitis who recovered completely. Treatment commonly consists in the exhibition of hypnotics to control the convulsions, venesection, spinal puncture, and the intravenous injec-

tion of hypertonic solutions of glucose or sodium thiosulphate, but it is doubtful whether anything has much effect upon the course of the disease.

### CONCLUSIONS

Three cases of hemorrhagic encephalitis are recorded in women near term or shortly after delivery, when the disease closely resembles eclampsia, in that it is commonly associated with convulsions and coma.

From our experience and from a review of the literature, it seems that pregnant women are more susceptible to the deleterious, as well as to the beneficial, effects of antisyphilitic treatment by the modern arsenicals than are other individuals. This susceptibility is more marked (1) during the first course of therapy, (2) in latent rather than in early syphilis, and, (3) in the last trimester of pregnancy.

The clinical picture, as we have observed it, was varied and may be confusing, but positive diagnosis can be made by pathologic changes in the central nervous system, more especially by the presence of scattered punctate hemorrhages around the smaller vessels, and usually by an associated edema.

Treatment was of little avail, death occurring within three days after the first toxic manifestations in each of our cases. Intelligent prophylaxis demands that great care be exercised in giving a first course of antisyphilitic arsenical therapy to a woman with latent syphilis in the latter months of pregnancy.

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## THE THERAPEUTIC VALUE OF ANTUITRIN-S IN MENOMETRORRHAGIA

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IN RECENT years no aspect of medicine has interested the profession to a greater degree than that relating to the function of the glands of internal secretion. Particularly in gynecology the advance in our knowledge has helped to give us a better understanding of the physiology of the generative organs. The demonstration of an ovarian active principle, the female sex hormone, in the circulating blood by Frank and his coworkers<sup>1</sup> and almost simultaneously by Loewe<sup>2</sup> represented the beginning of the modern advances. Further impetus was given hormonal studies in this field by the work of Allen and Doisy<sup>3</sup> who established the biologic test for the female sex hormone, and by Aschheim-Zondek<sup>4</sup> who isolated the prepituitary hormone. Since that time the volume of work has become so vast that it is almost an impossibility to follow the extensive literature that has arisen. Although the facts already established have helped our understanding of the physiology of the female genital tract, much remains to be cleared up. It is heartening to observe that the preponderance of published work is the result of laboratory experimentation. From the clinical angle attempts are being made to apply various hormone preparations found active in laboratory animals to human beings. The results published have already implanted in the mind of the medical profession to a considerable degree the usefulness of various endocrine preparations on the market at the present time. That they are extensively used is evident.

In previous papers<sup>5, 6</sup> we published our observations on the clinical results from the use of amniotin and theelin in the menopause. Some patients were improved but most were not. The only really favorable results were obtained in kraurosis vulvae where female sex hormone preparations definitely gave relief from itching during the period of treatment. In the discussion of a paper by E. Novak at the American Gynecological Society, one of us (S. H. G.) reported 24 cases of menometrorrhagia treated with antuitrin-S with no striking therapeutic effect.

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We wish at this time to report the results obtained with antuitrin-S\* in 14 additional cases of menometrorrhagia; the preparation, antuitrin-S titers, in the fresh state, to 100 R.U. per c.c. In all, 14 patients were treated for a period of three months. The substance was given by intramuscular injection 3 times weekly beginning with a dose of 3 c.c. per injection. Greater doses did not seem to us to be justifiable, especially as almost without exception the patients complained of fever and generalized pains after receiving large doses. The cases were selected with the express purpose of determining the efficacy of the preparation used, and for that reason no other therapy was given, with the possible exception of hygienic measures instituted in 2 cases. The series was limited because the cases were selected to rule out any lesion other than that associated with true functional menometrorrhagia.

### RESULTS

The results are classified according to the improvement noted. Table I shows the essential data. For the sake of accuracy those patients who showed even the slightest improvement were recorded as "improved." Actually, 2 patients were definitely benefited (M. C. and H. E.). The rest either were not relieved of the bleeding or the relief was negligible. It can be seen that here impersonal interpretation may be exceedingly difficult, and that a rigid sense of values must be brought into play to arrive at acceptable conclusions.

Of the 2 cases showing definite improvement, one (M. C.), was a virgin, eighteen years old, who had bled continuously for thirty-three days before treatment was begun, and who stopped bleeding almost immediately after the injections were instituted. Relief was striking. Of greater interest, however, is the fact that the patient remained amenorrheic for three and one-half months, even after treatment was discontinued. The other patient who showed definite improvement (H. E.) was forty-five years old, was markedly asthenic, and here general hygienic measures had to be included as part of her treatment. Of the remaining patients, 7 were not at all improved, and the other 5 were only slightly relieved. To qualify the term "slight improvement," it may be mentioned that it refers to shortening of the duration of the periods of bleeding to a minor extent. It cannot under any circumstances be interpreted as demonstrating an actual beneficial effect.

### DISCUSSION

As has been mentioned, in our series only 2 cases showed definite improvement. The first (M. C.) was amenorrheic for three and one-half months after treatment was begun. We wish to emphasize that cases of this type are very likely unduly to prejudice the physician in

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\*We are indebted to Parke, Davis & Co., for a liberal supply of the material.

TABLE I

PATIENT	AGE	PARITY	SYMPTOMS	PELVIC FINDINGS	NUMBER OF INJECTIONS AND DOSE	RESULTS	REMARKS
G. K.	25	0	Menometrorrhagia	Uterus slightly enlarged and thick	24 injections up to 6 c.c.	Improved at first. Bleeding recurred	Initial improvement then recurred
A. D.	23	0	Menometrorrhagia	Small, hypoplastic uterus otherwise negative	10 injections up to 6 c.c.	No improvement	Patient subsequently stopped bleeding spontaneously
L. P.	44	x	Metrorrhagia	Essentially negative	24 injections up to 6 c.c. per injection	Very slow improvement	Patient became pregnant while under treatment
M. C.	18	0	Metrorrhagia	Virgo essentially negative later cystic right ovary felt	30 injections up to 6 c.c.	Stopped bleeding. Improved	B o c a m e completely amenorrheic for three and a half months
R. D.	44	ii	Metrorrhagia	Irregular scarring of cervix. Uterus slightly enlarged	37 injections up to 6 c.c.	No improvement	
D. E.	45	iii	Menorrhagia	Essentially negative	30 injections up to 6 c.c.	No improvement	
I. B.	34	0	Metrorrhagia		38 injections up to 6 c.c.	No improvement	
P. S.	40	vii	Menorrhagia	Essentially negative	29 injections up to 6 c.c.	Slight improvement	Patient had menopause
H. E.	45	0	Metrorrhagia	Essentially negative	14 injections up to 6 c.c.	Improved	Patient markedly asthenic. Received general hygienic treatment as well
M. M.	34	i	Menometrorrhagia	Right adnexa slightly cystic	30 injections up to 6 c.c.	Improved at first then bleeding recurred	
G. N.	26	v	Metrorrhagia	Ventrotfixed uterus, otherwise negative	42 injections up to 6 c.c.	Some improvement	Patient asthenic. Improvement associated with general hygienic measures
J. N.	36	ii	Menorrhagia	Retroversion	20 injections up to 6 c.c.	No improvement	
R. S.	46	0	Metrorrhagia	Essentially negative	34 injections up to 6 c.c.	No improvement	
M. R.	30	ii	Menorrhagia	Slightly enlarged uterus	9 injections up to 4 c.c.	Very slight improvement if any	

favor of any material which he may use. There is a tendency to forget that such a cycle of events may occur without treatment of any kind. The "coincidence" factor must not be regarded too lightly. In the other case that showed marked improvement, hygienic measures which were included in the treatment due to the patient's marked asthenia, may have played more than a casual rôle.

In contrast to the above series, we wish to call attention to a control group of menometrorrhagia cases which have shown improvement under a regime of such simple measures as ergot, short-hot douches, or following no active treatment at all. We emphasize this because the factor of coincidence, as had been mentioned, is of great importance.

It is interesting to note that our results are in marked variance with reports to be found in the literature. Prior to 1925, there are repeated references to the efficacy of endocrine preparations long since proved inert. The era when "corpus luteum extract" was in vogue is also not too remote. The use of prepituitary and female sex hormone preparations is the latest development. Careful scrutiny of the literature brings to light facts which are not only interesting but also actually astounding when subjected to analysis. Tables II, III, and IV represent a cross-section of the recent literature and are fairly representative of the claims made for various endocrine products. At the outset one is struck by the great variety of conditions in which the prepituitary and female sex hormones have been applied. Although these preparations properly belong to the gynecologic field, it is astonishing to see that not only are they in use in entirely unrelated conditions, but also good results are actually reported. Thus Bengston<sup>7</sup> and Kohn<sup>8</sup> have found the prepituitary hormone efficacious in alopecia, practically always in males.

In the abnormalities of the female genital system the reports are on the whole, favorable. In the amenorrheas and oligomenorrheas, as Table II shows, the hormone preparations have apparently helped to regulate the cycle to a greater or lesser degree. The results, however, are far from conclusive. For example, Sevringhaus and Thornton<sup>9</sup> report improvement in 10 of 23 patients treated with follutein or antuitrin-S. From such a report some doubt as to the value of the therapy must certainly be entertained. Female sex hormone preparations alone have yielded somewhat better results, which probably accounts for the present popularity of this material in amenorrheic states. However, even if it were possible to produce menstruation by the use of hormone preparations in all cases, it is questionable whether the constant injections necessary are justifiable. In our opinion careful explanation of the individual's condition, with reassurance and perhaps advice as to general hygiene should be all that is necessary. Occasionally a marked asthenia, hypothyroidism, or obesity is found to be the underlying cause of the amenorrhea. One of us (S. H. G.)<sup>10</sup>



TABLE II. RESULTS OF USE OF FEMALE SEX HORMONE IN VARIOUS CONDITIONS

AUTHOR	MENOPAUSE	AMENOR- RHEA	KRAUROSIS	HABITUAL ABORTION	MENO- METROR- RHAGIA	DYSMENOR- RHEA	PSYCHO- NEUROSIS	HEMO- PIELIA	STERILITY
Geist and Spielman <sup>3, 6</sup>	Equivocal results	Poor	Temporary relief of itching						
Sevringhaus and Thornton <sup>9</sup>	Good								
Johnstone, Wiesner, and Marshall <sup>14</sup>		Good		Good	Good				
Ehrhardt <sup>15</sup>		Good 70%			Good				
Hamblen <sup>16</sup>	Good	Good				Good	Good 30%		
Schmidt and Anselmino <sup>17</sup>	Poor	Poor	Good in eczema						
Barack <sup>20</sup>	Good	Good							
Hall <sup>21</sup>	Good	Good							
Birel <sup>22</sup>								Good	
Stetson, Forkner, Chew, Rich <sup>23</sup>								Poor	
Hirst <sup>24</sup>									Good in 5 of 12
Szego <sup>25</sup>			Good in eczema						

TABLE III. ANTERIOR PITUITARY-LIKE HORMONE IN VARIED CONDITIONS

AUTHOR	MENO- METRO- RRIAGIA	ALOPECIA	AMENORRHEA	HIRSUTIES	DYSMENOR- RHEA	HABITUAL ABORTION	BREASTS	PSYCHIC
Geist and Spielman <sup>5, 6</sup>	Poor results							
Bengston <sup>7</sup>		Good results						
Seyringhaus and Thornton <sup>9</sup>			Good in 50 per cent	Poor results				
Laroche and Simmonet <sup>12</sup>			Good		Good			
Novak <sup>13</sup>	Good results		Good in some					
Johnstone, Wiesner, Marshall <sup>14</sup>	Good F. S. H. and A. P. R.		Good result F. S. H. and A. P. L.			Good results F. S. H. and A. P. L.		
Ehrhardt <sup>15</sup>	Good F. S. H. Equivocal A. P. H.		Good				Galactagogue	
Hamblen <sup>16</sup>	Equivocal		Good F. S. H. and A. P. L.					Good 30 per cent
Witherspoon <sup>18</sup>						50 per cent good		
Barach <sup>20</sup>	Good results climacteric		Good F. S. H. and A. P. L.					

in a study of normally menstruating women has pointed out the marked variations in the menstrual cycle which may occur in perfectly healthy young women. Fluhmann<sup>11</sup> also calls attention to these variations.

In the menometrorrhagias the results are conflicting. Laroche and Simmonet<sup>12</sup> warn against using the prepituitary hormone, while Novak<sup>13</sup> finds it useful. Johnstone, Wiesner, and Marshall<sup>14</sup> obtain improvement with a combination of anterior pituitary and female sex hormone, while the results of Ehrhardt<sup>15</sup> and of Hamblen<sup>16</sup> are equivocal. Schmidt and Anselmino<sup>17</sup> do not find hormonal therapy efficacious in menstrual disturbances, but obtain good results in climacteric eczema, urticaria, pemphigus, pruritis, and arthritis deformans. These varied opinions are only mute testimony to the fact that hormonal therapeutics at the present time leaves much to be desired. It may be mentioned in passing that we believe that snake venom therapy as reported by Peck and Goldberger<sup>19</sup> in functional bleeding is probably the most efficacious treatment in use at the present time.

TABLE IV. COMPARISON BETWEEN RESULT OF TREATMENT IN SIMILAR CONDITIONS WITH DISSIMILAR SUBSTANCES

AUTHOR	MENO- METROR- RHAGIA	AMENOR- RHEA	HABITUAL ABORTION	DYSMENOR- RHEA	PSYCHIC SYMPTOMS
Geist and Spiel- man <sup>5, 6</sup>	Poor A. P. L.	Poor F. S. H.			
Novak <sup>12</sup>	Good A. P. L.	Good in some A. P. L.			
Hamblen <sup>16</sup>	Equivocal A. P. L.	Good F. S. H. and A. P. L.		Good F. S. H.	30% good F. S. H. and A. P. L.
Johnstone, Wiesner, Marshall <sup>14</sup>	Good F. S. H. and A. P. L.	Good F. S. H. and A. P. L.	Good F. S. H. and A. P. L.		
Ehrhardt <sup>15</sup>	Good F. S. H. Equivocal A. P. L.	Good F. S. H. Good 70% A. P. L.			
Schmidt and Anselmino <sup>17</sup>		Poor F. S. H.			
Barach <sup>20</sup>		Good F. S. H.			
Hall <sup>21</sup>		Good F. S. H.			
Serringhaus and Thornton <sup>9</sup>		Good 50% A. P. L.			
Laroche and Simmonet <sup>12</sup>		Good A. P. L.		Good A. P. L.	
Witherspoon <sup>18</sup>			Good A. P. L.		

Little need be said regarding the other conditions treated and favorably reported upon. Witherspoon<sup>18</sup> used the prepituitary hormone in 12 cases of threatened abortion treated in the hospital, where his criteria of suitability for treatment were "cramps, uterine bleeding, and two finger dilatation of the cervical os, through which the uterine contents can be palpated." Six of the 12 patients aborted while under treatment. He claims 50 per cent cures although of the "cures" 4 patients subsequently aborted after leaving the hospital. In habitual abortion Johnstone, Wiesner, and Marshall<sup>14</sup> obtained good results with both hormones. The patients, however, were kept in bed during the interval of the expected periods. Such reports are misleading.

For any therapeutic measure to be acceptable, exact and unquestioned results must be obtainable in a high percentage of cases. When sex hormone preparations can show the definite and striking effects in the human being that insulin, adrenalin, and pituitrin do, then and then only may they be welcomed as part of the physician's armamentarium.

#### SUMMARY AND CONCLUSIONS

1. In 14 cases of menometrorrhagia exhibition of the prepituitary-like hormone in the form of antuitrin-S was associated with improvement in two cases only.

2. A survey of the literature shows such varied and conflicting opinions, that the present widespread use of "endocrine" products in menstrual disturbances seem to us to be unwarranted.

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100 EAST 74TH STREET

145 WEST 86TH STREET

# THE ORIGIN OF CHORIONEPITHELIOMAS AND OF EMBOLI FROM TROPHOBLASTIC FRAGMENTS ENCLOSED IN THE MYOMETRIUM

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SINCE the early writings of Säger<sup>1</sup> concerning that type of neoplasm which he chose to term "deciduoma malignum," there have been frequent appearances in the medical literature of articles relating to this subject. In 1898 et seq. Marchand's noteworthy contributions<sup>2, 3</sup> greatly clarified the field by quite conclusively demonstrating the placental origin of this neoplasm. He indicated the striking similarity between the neoplastic cells composing the tumor and the syncytial and Langhans cells of normal chorionic villi, and designated the neoplasm "chorionepithelioma." Recently, reports<sup>4, 5, 6</sup> of positive Aschheim-Zondek reactions obtained from the urine of patients with chorionepithelioma have proved further the close relationship between this neoplasm and normal placental tissue.

Numerous articles<sup>7, 8, 9, 10</sup> offering a study of the pathogenesis of chorionepithelioma by means of various case reports have established the clinical manifestations of the disease. Most of these patients have presented neoplastic tissue easily accessible for biopsy. An examination of tissue curetted from the uterus has established the diagnosis of chorionepithelioma. However, certain patients, afflicted with this neoplasm, have not been adaptable to this type of study. Uterine curettements have failed to reveal neoplasm. Consequently, the condition has been misinterpreted, and therefore mismanaged. We propose to review two cases of this type, indicating the inherent possibilities of error in diagnosis and resultant mismanagement, with the hope that subsequent similar situations will be approached more intelligently.

CASE 1.—Clinical Report: E. H., white, twenty-nine years of age, unmarried, entered the hospital Nov. 19, 1931, with the complaint of vaginal bleeding. An appendectomy and right salpingo-oophorectomy was done in 1926 and a tonsillectomy in 1928.

Menstruation began at seventeen, flow usually moderate, of about three days' duration, and not accompanied by pain. The interval between menses varied from four weeks to six weeks. The patient denied any pregnancies but admitted frequent coitus prior to May, 1931. She denied sexual intercourse after this date.

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The last menstrual period which seemed normal to the patient occurred July 15, 1930. The patient stated that a physician who examined her subsequent to this time told her that she was not pregnant. Prolonged periods of bleeding with short irregular intervals of quiescence followed.

In November of 1930, the patient suddenly had a profuse hemorrhage, severe enough to make her very weak. From this time until July, 1931, there were irregular periods of amenorrhea varying in length from four to six weeks with intervening periods of profuse menorrhagia lasting as long as ten days. After the first part of July, 1931, the uterine bleeding became continuous.

In September, 1931, the patient visited a physician and a dilatation and curettage were done, but the menorrhagia continued. These curettings were not examined by a pathologist.

Examination of the patient in the hospital revealed the following: pallor, weakness, well-healed right rectus scar, tenderness over lower abdomen especially in midline, a marital vaginal outlet, a firm cervix of normal size, a small freely movable firm uterus, and palpably normal adnexa. Dilatation and curettage yielded abundant uterine tissue diagnosed histologically as hyperplasia of the endometrium. The blood showed 70 per cent hemoglobin, 3,380,000 erythrocytes, and 8,400 leucocytes. The patient was discharged Nov. 28, 1931, without an adequate explanation of the menorrhagia.

She was re-admitted Dec. 31, 1931, complaining again of vaginal bleeding. During the interval menorrhagia had been continuous, requiring the use of 24 pads weekly. The patient had been unable to work because of shortness of breath and weakness.

Examination now revealed marked pallor. There were tubular breath sounds at the right base. Marked presystolic and systolic murmurs could be heard over the precordia, and most distinctly over the aortic area. Blood pressure 100/70. Pulse rate 104. There was tenderness on deep pressure in both lower quadrants. The corpus uteri seemed to be of normal size but the cervix was enlarged and irregular. The adnexa were normal to palpation. A necrotic mass of tissue 2 to 3 cm. in diameter was removed from the cervical canal. Sections of this material were diagnosed typical chorionepithelioma.

On Jan. 2, 1932, the hemoglobin was 55 per cent (Sahli) and erythrocytes 2,560,000. On Jan. 4, 1932, the patient was given a transfusion of 425 c.c. of blood, following grouping of both patient and donor as well as establishing specific compatibility. Laparotomy was done Jan. 12, 1932, and the uterus, without adnexa, extirpated. Friedman's modification of the Aschheim-Zondek test, using a pre-operative urine specimen, was reported January 14 as "strongly positive."

On January 15, the patient's condition was such that another transfusion was indicated. Blood compatibility tests were again carefully performed and a donor of a homologous group (IV Moss) was employed. At 5:30 P.M., the major part of 550 c.c. of blood had been given when she complained of abdominal pain which increased in severity. The procedure was abruptly terminated. However, the abdominal pain continued, became cramplike, and was referred to the hips. Adrenalin gave temporary relief. Later in the evening, cyanosis and profuse diaphoresis developed. Stimulants failed. The pulse became "thready and weak," respirations were labored, cyanosis increased and death occurred at 11:30 P.M., Jan. 15, 1932.

*Pathologic Examination of Uterus.*—The uterus measured 8 cm. from the external os to the superior border of the fundus and 5 cm. in its greatest diameter which was 2 cm. above the external os. The external surface showed no gross evidence of neoplasm.

A sagittal section of the uterus (Fig. 1) revealed a hemorrhagic polypoid mass extruding from the posterosuperior wall down into the uterine cavity. The lower portion of the mass presented at the widely dilated external os. The mass was

roughly round with a diameter of 4 cm. The diameter of the external os was 1.5 cm. This hemorrhagic polypoid tumor blended into the myometrium; being separated from the lumen of the uterus by a definite covering of endometrium and a thin layer of myometrium. This surface layer was ulcerated at the extreme inferior portion of the mass. The remainder of the uterus appeared to be uninvolved by neoplasm.

Microscopic sections made from tissue taken deeply in the tumor nodule (Fig. 2) showed the typical malignant chorionepithelioma of Marchand<sup>2</sup> or of the chorio-



Fig. 1.—Case 1. A sagittal section of the uterus, revealing the hemorrhagic mass of chorionepithelioma extruding from the posterosuperior wall, everting the overlying myometrium and endometrium. Five-eighths natural size.



Fig. 2.—Case 1. A section of tissue taken deeply in the polypoid mass, showing typical chorionepithelioma.  $\times 400$ .

carcinoma of Ewing's classification.<sup>11</sup> Sections through the surface of the mass demonstrated an intact endometrial covering and a narrow zone of myometrium (Fig. 3).

**Necropsy Report.**—A complete postmortem examination was made Jan. 16, 1932. Nothing could be found to substantiate the clinical hypothesis that the final symptoms of the patient were caused by a transfusion with incompatible blood. *Staphylococcus pyogenes aureus* was cultured from blood removed from the right auricle. The gross and microscopic studies of the tissues confirmed the diagnosis of septicemia.

A small hemorrhagic firm nodule, measuring 1 by 0.7 by 0.8 cm. was situated

deeply in the parenchyma of the lower lobe of the right lung. Gray granular tissue was intermingled with the hemorrhagic material. This was the only remaining evidence of chorionepithelioma that could be found.

The left fallopian tube and ovary were present, but these structures were absent on the right. Corpora hemorrhagica or corpora lutea were not reported.

Microscopic study of the lesion in the lung (Fig. 4) revealed a mass of hyalinized fibrin and erythrocytes with intermingled tissue of placental origin. One distinct cross-section of a chorionic villus partially covered with a single layer of Langhans cells and a small mass of syncytium was present. Longitudinal sections of less definite bulbous chorionic villi were seen. A few small collections of Langhans and



Fig. 3.—Case 1. A section through the surface of the polypoid mass, demonstrating the intact endometrium over the chorionepithelioma.  $\times 400$ .



Fig. 4.—Case 1. Section of the hemorrhagic nodule in the lung. Note the embolic chorionic villus, cut in cross-section, surrounded by fibrin and erythrocytes. Observe the retrogressive appearance of its Langhans and syncytial cells. A villus, cut longitudinally, is present in the lower left of the field. Beneath it are partially collapsed pulmonary alveoli.  $\times 80$ .

syncytial cells, not attached to villi, were demonstrable in the fibrin and in the marginal lung parenchyma. The entire lesion appeared distinctly retrogressive.

**CASE 2.**—A. T., white, forty-two years of age, married, entered the hospital in April, 1932, complaining of hemorrhages from the vagina.

The menstrual history was not unusual. The first pregnancy was in 1918. It advanced to full term and resulted in a normal delivery. The second pregnancy terminated with the birth of a normal boy Nov. 12, 1926. This pregnancy was complicated by severe pyelitis, from which the patient gradually recovered following the delivery. The pyelitis recurred for a brief interval in 1928.

Menses remained normal and regular following the pregnancy in 1926, until Sept. 1, 1931, the date of the last menstruation that preceded a period of amenorrhea



which extended through September and October. At the end of October, the patient had a profuse hemorrhage which her doctor diagnosed as an abortion. The uterus was not curetted. Almost constant uterine bleeding, described as "a dirty discharge with a little old brown blood," occurred during the following five months. On April 1, 1932, she had another severe hemorrhage.

The patient was pale and weak. The uterus was tender and less movable than normal. The blood showed 4,000,000 erythrocytes and 75 per cent hemoglobin. Material removed from the uterus by curettage was reported as "no evidence of malignancy."

During an exploratory operation, as the uterus was being carefully manipulated, a very severe sudden hemorrhage occurred. The uterus was removed. In the lateral wall of the pelvis and involving the culdesac the surgeon observed what he described as "brown dead tissue, which could not be completely removed—part of the peritoneum and underlying cellular pelvic tissue, evidently necrotic."

Following the operation, the patient made a very satisfactory recovery. Several



Fig. 5.—Case 2. A sagittal section of the uterus showing the nodules of chorion-epithelioma in the myometrium, separated from the normal uterine cavity by a thick layer of smooth muscle. Note the inaccessibility of the neoplasm to the curette. Natural size.

subsequent examinations were negative. Specimens of the patient's urine were submitted Jan. 24, 1934, and Feb. 9, 1934. Friedman's modification of the Aschheim-Zondek test resulted in a negative reaction with each of these specimens of urine.

*Pathologic Examination of Uterus and Left Adnexa.*—Around the left cornu of the uterus, extending into the broad ligament, was hemorrhagic appearing tissue which was not necrotic but was viable. The ovary measured 2.7 by 1.5 by 1.2 cm. It contained a corpus luteum 1.0 cm. in diameter. The uterus was globular, measuring 6.3 cm. superoinferiorly, 5.0 cm. anteroposteriorly, and 5.0 cm. laterally.

A sagittal section through the uterus (Fig. 5) showed the lumen to be of normal size, shape, and position, lined by smooth endometrium which showed no evidence of neoplasm. The anterior wall was 2.0 cm. thick and the posterior, 2.8 cm. A nodule of abnormal tissue, measuring 1.7 cm. anteroposteriorly and 2.8 cm. superoinferiorly, was situated in the posterior wall. This tissue was composed of thin-walled vesicle-like structures intermingled with grey granular tissue. The nodule, at its closest

point to the lumen, was separated from the endometrium by 0.6 cm. of myometrium. Extending from this nodule through the left uterine cornu into the broad ligament were small vesicles similar to those composing the main tumor mass. A smaller nodule of similar tissue, measuring 0.4 cm. in diameter, was situated in the lower uterine segment in the posterior wall, deeply in the myometrium.

Microscopic study of a section of the broad ligament near its attachment to the left cornu of the uterus revealed several thick-walled dilated veins filled with large bulbous, villous structures. The villi were ensheathed with a thick layer of Langhans and syncytial cells, the latter predominating. Fibrin, with intermingled erythrocytes and leucocytes, partially covered the surface. At some points, the villi were attached to the vessel wall, and, in a few places, the chorionic epithelium seemed to invade the wall. The remaining connective tissue of the broad ligament showed infiltration with fibrin, erythrocytes, and leucocytes, including many polymorphonuclear neutrophils.

A section of the hemorrhagic material deposited about the uterus and the broad ligament showed syncytial and Langhans cells and an occasional villous structure intermingled with fibrin, erythrocytes, and leucocytes.



Fig. 6.—Case 2. Edematous chorionic villi, ensheathed by proliferating syncytial and Langhans cells, composing the nodules in the myometrium.  $\times 80$ .

A study of the histology of the nodule situated in the myometrium (Fig. 6) revealed edematous chorionic villi with sheaths of syncytial and Langhans cells. There was demonstrable invasion by chorionic epithelium of the surrounding smooth muscle. The adjacent myometrium showed acute inflammation and partial necrosis.

#### DISCUSSION

The histories of the two cases were similar in many respects. Both were white females of the menstrual age who sought medical attention because of excessive vaginal bleeding. The records indicated an initial period of pregnancy of about three months' duration for the first patient and quite definitely two months for the second. In each case, amenorrhea was terminated by a severe hemorrhage apparently the result of abortion. Careful investigation failed to reveal that material resembling mole was expelled by either patient. Irregular vaginal bleeding, intermittent in the first case, and remittent in the second, followed for fourteen and five months, respectively. Each patient

complained of discomfort in the lower abdomen. Palpation of the uterus elicited tenderness. Both showed definite clinical and laboratory signs of loss of blood. Uterine curettage failed to explain the menorrhagia of either patient, although late in the course of the first (after fourteen months), material extruded from the cervical canal was diagnosed chorionepithelioma. Hysterectomy was performed in both cases, and study of the uteri resulted in diagnoses of chorionepithelioma. The evidence was conclusive that the neoplasm found in each uterus originally had been encased in the myometrium, a sufficient distance from the endometrium to be inaccessible by curettage.

The mechanism of the development of chorionepithelioma in this site seems relatively obvious. Following the brief period of pregnancy, the endometrium rapidly extended over the placental site, entrapping bits of trophoderm located deeply in the myometrium. Such placental remnants are not uncommon.<sup>15</sup> Usually they are rapidly absorbed, but they may lie dormant for long intervals, chorionic villi having been found in the uterine wall eighteen years after the last pregnancy.<sup>16</sup> As chorionepithelioma has its origin from placental tissue, it seems fair to assume that entrapped portions of trophoderm might give rise to newgrowths at any time.<sup>17</sup>

The neoplasm initiated in the myometrium progresses along the lines of least resistance. If its location is near the lumen of the uterus, as the newgrowth increases in size, it tends to evert the mucosa and become a polypoid mass consisting of chorionepithelioma covered by endometrium and a thin layer of myometrium. Necrobiosis of the enveloping tissue leads to ulceration, and the neoplastic mass finally becomes accessible to the curette. Our first case illustrates this type of development. Should the newgrowth arise deeply in the wall, such eversion of the endometrium is not probable. The neoplastic tissue is now likely to extend along the vascular channels toward the broad ligament.<sup>18</sup> Such a manifestation of the disease was present in our second case.

The literature revealed other cases of chorionepithelioma occurring in the myometrium in a position inaccessible to curettage.<sup>10, 11, 19, 20, 21, 22, 23</sup> Some of these case reports described additional tumor tissue that was superficially available, but the accounts suggested that the primary neoplasm originated intramurally and probably remained in this location for some time, delaying a diagnosis based on the study of uterine curettings.

The morbid anatomy of the two neoplasms presented is not identical. The histopathology of the first is definitely that of the typical malignant chorionepithelioma of Marchand<sup>2</sup> or of the choriocarcinoma of Ewing's classification.<sup>11</sup> No one will question the very malignant appearance of this tumor. We also have made the diagnosis of "chorionepithelioma" in the second case. A tumor that has invaded the wall of the uterus, proliferated there, and extended along the uterine veins far into the broad ligament must be considered malignant.<sup>24</sup> We have not subdivided malignant placental neoplasms as Ewing<sup>11</sup> has recommended. However, it is our opinion that this tumor would qualify for his less malignant group, "chorio adenoma destruens." The present good health of the patient, in spite of the reported incomplete surgical removal of the neoplastic tissue and the demonstration of neoplasm in large veins, is in accord with Ewing's predictions for this type of case. The repeatedly negative Friedman tests obtained with the patient's urine indicate that viable placental neoplasm is not present in any of her tissues.

The reports of Sampson,<sup>12</sup> Ries,<sup>16</sup> Mestitz,<sup>13</sup> and Hansmann and Schenken<sup>14</sup> indicate that the large vascular channels of the myometrium are quite accessible during normal pregnancy. Schmorl<sup>25</sup> and Dunger have found trophoblastic pulmonary

emboli in the lungs of women during pregnancy uncomplicated by placental neoplasm. If normal chorionic villi can erode vessels and become emboli to distant organs, it is not surprising that malignant neoplastic tissue derived from placenta should progress in a similar manner. The minute metastases, some of them in vessels, described in our two cases are examples of this mechanism of dissemination. Metastasis of chorionepithelioma by means of small emboli is probably the common method of extension to broad ligament, vagina, vulva, and lung.

The retrogressive appearance of the solitary metastatic lesion found in the lung of our first patient suggests rather interesting speculations. The histology of this lesion is in sharp contrast to that of the actively proliferating mass in the uterus. Two possible theories are offered. The lesion may be a true neoplastic metastasis, and, as such, an example of the pathology in the reported chorionepithelioma metastases that have disappeared following hysterectomy.<sup>10, 15</sup> If this view is accepted, the case is an exception to Ewing's statement<sup>11</sup> that "there is no satisfactory evidence in the literature that metastases of tumors of this histologic type (choriocarcinoma) have ever spontaneously regressed."

Our second theory, and the one which we favor, assumes that the pulmonary lesion is the result of a nonneoplastic trophoblastic embolus of the type described by Schmorl.<sup>25</sup> An embolus of this nature, containing sufficiently viable cells to soften and rupture a vessel in which it lodged, could cause a pulmonary hemorrhage with consequent hemoptysis. If this occurred in a patient with a recognized chorionepithelioma of the uterus, the attending physician would be very likely to diagnose pulmonary metastasis and give his patient a more grave prognosis. If hysterectomy removed the chorionepithelioma, the patient might recover. In such an event, the clinician would probably interpret the case as a cure following hysterectomy for chorionepithelioma with metastasis. But, as we have indicated, the lung lesion would not be actually neoplastic.

#### SUMMARY

1. Two cases of chorionepithelioma have been presented in which the tumor apparently originated deeply in the myometrium. This location of the neoplasm made it inaccessible to the curette and consequently retarded the diagnosis.

2. The Aschheim-Zondek reaction or Friedman test should be an especially valuable aid to early diagnosis of chorionepithelioma of the intramural type.

3. Clinical symptoms suggesting chorionepithelioma, together with a strongly positive Aschheim-Zondek reaction or Friedman test, yet no evidence whatever of placenta or placental neoplasm in uterine curettements, should indicate surgical exploration. Such a procedure may often result in the early diagnosis and adequate treatment of an intramural newgrowth of placental origin.

4. A retrogressing hemorrhagic pulmonary lesion containing placental tissue has been described; and the disappearance of pulmonary metastases of chorionepithelioma has been discussed.

5. The probable mechanism of metastasis of chorionepithelioma has been explained.

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Von Szathmary: Brenner Tumors in the Walls of Ovarian Cysts, Arch. f. Gynäk. 154: 390, 1933.

The author reports five Brenner tumors all cystic in character, thus falling into the second group according to R. Meyer. This is unusual, since the second group is the smaller of the two groups into which this uncommon type of ovarian tumor can be classified. They are entirely different from granulosa cell tumors, since they are both histologically and clinically benign. They apparently have no effect upon the uterus; myomas are frequently found in association with them. These tumors definitely arise from the epithelial elements of Walthard's cell groups.

RALPH A. REIS.

McKinney, Stewart, and McClure: Suppurative Ovaritis Following Mumps, Lancet 2: 22, 1934.

There is only one other report of suppuration in the ovary in association with mumps. The patient ran a febrile course, developing a mass in the lower left iliac fossa. Twelve days later when vomiting began the abdominal cavity was drained. The left ovary was found necrotic, and only one-sixth of the right was conserved. A few adhesions involved the tubes. The uterus was retroverted. The appendix was normal.

Three weeks later the patient was discharged from the hospital in good condition.

II. CLOSE HESSELTINE.

## ANALYTICAL STUDY OF CESAREAN SECTIONS IN A HOSPITAL SERVICE OF 9,000 DELIVERIES\*

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WHAT are proper indications for cesarean section?" The answer to this question must be conditioned by adequate recognition of involved maternal and fetal morbidity and mortality. The operation was originally advised for the extraction of a baby whose life was of primary concern, but now we also expect to secure the mother against immediate or consequential damage. While the various operative procedures have been fairly well standardized, perfection in technic constitutes but one of many factors bearing upon morbidity and mortality. Why an operation of relatively easy performance should carry the highest reported morbidity and mortality of any uncomplicated pelvic-abdominal operation is not easy to understand. The reason must be less in the operation than in the failure properly to interpret or evaluate the attendant general and obstetric facts regarding the patient. Obstetric judgment is no less important than good obstetric therapy. They are inseparably necessary for satisfactory results.

Our purpose is to record the factors and results attendant upon the performance of cesarean section in a large maternity hospital during a two-year period among 9,000 deliveries. It serves as a basis for critical analysis of reasons and results, with consideration of other contingent data not given statistically. The aphorism that statistics speak the language of the analyst is negated by defining standards, as for the morbidity tables, and supplying incidental data which might have any influence upon those recorded.

### INCIDENCE OF CESAREAN SECTION

There were 177 cesarean sections, representing 2 per cent of 8,852 deliveries in the Margaret Hague Maternity Hospital during a twenty-four-month period up to October, 1933. Thirty-three patients who aborted in the first trimester of pregnancy and 115 who miscarried in the second trimester are deducted from the 9,000 for quite obvious reasons.

Without analyzing at this time the indications for section, it must be noted that of the 177 operations performed, 26 were done on patients who had previously had cesarean sections. This does not mean that we blindly accept the conservative and generally sound dictum of "once a cesarean, always a cesarean." When a

\*Presented before the Academy of Medicine of Northern New Jersey, Newark, N. J., November 2, 1933.

patient has previously had a low transverse laparotrachelotomy operation, without morbidity, and where the primary indication did not preclude the possibility of subsequent relatively easy vaginal delivery, a mild trial labor is permitted, and in our experience many such patients deliver spontaneously. There was no mortality in this group, although one ruptured uterus occurred. Of the 177 sections performed, 151 were upon patients not previously subjected to the operation.

Probably more important than resectioning patients is the occasion and incidence of cesarean section in women who have previously delivered, even with indifferent results, vaginally.

Fifty-six patients of the series had previously delivered vaginally, 31.6 per cent of the total. In their previous deliveries, of 28 patients with cephalopelvic disproportion, 17 or 60 per cent had delivered stillbirths. Of the others, 11 were sectioned because of placenta previa, 7 for cardionephritis and heart disease, 4 for abruptio placentae, 2 uterine tumors, and one each for brain tumor, tuberculosis, and stenosis following cervical amputation. These data are of importance, and yet they do not measure the persisting pelvic trauma still in evidence in many of this group, as a result of former obstetric experiences. Incidentally there were but 4 morbid cases among those sectioned after previous vaginal deliveries, a morbidity of 7 per cent.

#### INDICATIONS FOR OPERATION

The most frequent indication for section was contracted pelvis, totaling 100 or 56 per cent. Of these, 75 were generally contracted and 21 of the simple flat type. The next largest group, 26 in all, were patients who had previously been sectioned. The third largest group was composed of 15 cases of placenta previa, of which 9 were of the central type. Cardiac disease furnished the indication in 10 cases, and nephritis in 7.

Fibromyomatous uteri in 3, dystocia dystrophy syndrome in 2, and abruptio placentae in 5, and a scattering of 7 other indications with one case each.

In the resectioned cases *all* presented indications at the first operation which still militated against proper vaginal delivery. In this group, cephalopelvic disproportion rightfully assumed responsibility for 24 or 92 per cent of the total. It is evident that promiscuous use of the operation for varied indications is not existent.

#### EFFECT OF AGE AND PARITY

Age seems to have little effect on cesarean incidence. But if it is remembered that 55 per cent of the total operations were on primiparas and that while the vast majority of patients delivered during this two-year period were under thirty years of age, 40 per cent of these sectioned were over thirty, it is readily apparent that patients, especially primiparas beyond thirty years, have a distinctly greater chance of having pregnancy terminated by cesarean section.

#### RELATION OF OPERATIVE INDICATION TO MORTALITY AND MORBIDITY

Contracted pelvis was the most common indication, and here also was the highest morbidity rating, i.e., 14 or 14 per cent. The fetal mortality in this group was 7 or 7 per cent. The question arises whether in this most difficult group requiring the greatest judgment to handle, some of these patients were sectioned at a time and in a condition when they were not only more likely to influence morbidity rates, but were more apt to lose the baby as well.

Where patients had been previously sectioned, a total of 26, there were two instances of morbidity (7.7 per cent). There were no fetal deaths in this group. Thus

it appears that these patients protected from the hazards of a fruitless labor because of their previous experiences, have the happiest expectancy.

The placenta previa group shows the value of good judgment. Fifteen of 83 placenta previa patients delivered in two years were subjected to abdominal hysterotomy, an incidence of 1 to 5.5 (18 per cent). The results in this group were excellent, as there were no maternal deaths, and no morbidity. There were only 4 fetal deaths (only one beyond the eighth month of gestation), and 11 babies left the hospital in good condition. The operation in this group was reserved mainly for patients in whom vaginal delivery presented undue additional hazards, or for placenta previa with severe bleeding through an undilated cervix, especially in primiparas.

Ten patients with heart disease as the primary indication were operated upon, and one died within a day of cardiac failure. Her death was impending and the operation was undertaken mainly in the interest of the child, which survived. There was but one fetal death, and the results in this group of selected cardiac cases are considered satisfactory.

There was only one maternal death in 5 patients operated upon for abruptio placentae, and this proved to be uteroplacental apoplexy at operation. The fetal mortality was 100 per cent as would be expected. Only when maternal survival seemed incompatible with vaginal delivery was cesarean section resorted to in this group.

Only 2 patients were sectioned with preeclampsia as the primary indication and none for eclampsia. There was one fetal death (seven months, 790 gm. fetus, colored, ill nourished in a fibromyomatous uterus).

#### TYPE OF OPERATION

The operation chosen in 116 cases, or two-thirds of the total of 177, was the low cervical type laparotrachelotomy with the transverse incision popularized by Phaneuf. The DeLee or Hirst modification, through the lower segment and cervix, was done in 8 cases. Of the 35 classical sections done, 5 developed fever, as contrasted with a morbidity of 11 per cent in the laparotrachelotomy groups. Fifteen Latzko operations were performed in frankly or presumably infected cases, with no deaths, and 20 per cent morbidity. There were 5 deaths or 4.2 per cent in the Phaneuf operation, and two deaths or 5.7 per cent in 35 classical cesareans.

#### TYPE AND AMOUNT OF ANESTHESIA USED

One hundred and sixty-two of 177 patients had spinal anesthesia alone, and 7 spinal anesthesia with supplementary gas-ether. A majority of the spinal injections were performed by resident internes, and there were no anesthesia deaths. Three patients were given ether, and one died under the anesthetic. Four had local anesthesia alone and one avertin and local.

Primiparas having cesarean sections totaled 99 or 55 per cent of the total, the majority of the indications being cephalopelvic disproportion. Nearly all of the cases of nephritis and heart disease were in multiparas, while secundiparas and tertiparas claimed many of the group which should have had sections at first delivery or who had unexpected complications following previously normal vaginal delivery.

#### CONDITIONS AFFECTING MORBIDITY AND MORTALITY

It is apparent from Table I that it is quite safe to permit labor to proceed for a period up to twelve hours. It is likewise permissible to defer decision within twelve hours of rupture of the membranes. But following the "twelve-hour safe period," there is a rapid and precipitous climb in morbidity. It is not always possible to



apply this lesson to a given case, but the "twelve-hour safe period" should constantly occur to the obstetrician in considering factors bearing upon the manner of terminating pregnancy.

Vaginal examinations must not be done upon prospective section cases unless one is ready to accept a trebling of the morbidity rate. It is not our custom to make vaginal examinations; the rectum offers a digital check on labor progress. Vaginal examinations are reserved for cases where they seem clearly indicated or necessary and are made with the patient prepared as for delivery.

TABLE I. CONDITION AFFECTING MORBID AND FATAL CASES

## I. Membranes ruptured:

HOURS	TOTAL	MORBID	PER CENT	FATAL	PER CENT
0-12	120	5	4.2	5	4.2
12-24	14	3	21.4	2	14.3
24-38	12	4	33.3		
48 or more	8	3	37.5		
Not determined	23	7	30.4		

## II. Vaginal examinations:

NUMBER OF EXAMINATIONS	TOTAL CASES	MORBID	MORBIDITY PER CENT	FATAL
None or one	161	17	10.6	7
Two	13	4	30.8	
Three or more	3	1	33.3	

## III. Hours in labor:

HOURS	CASES	MORBID	MORBIDITY PER CENT	FATAL
0-12	90	4	4.4	4
12-24	37	4	10.8	1
24-48	36	8	22.2	2
48 or over	14	6	42.9	

After proper preparation, one vaginal examination is made routinely before abdominal section. On rare occasions it had led to change in type of interference. Rectal examinations, if unskillfully done, may be positively dangerous in patients with ruptured membranes where a severe cervicitis existed during pregnancy.

Thus it may be briefly stated that for best operative results, the patient should not be examined vaginally and should be operated upon within the "twelve-hour safe period" as regards hours of labor and duration of ruptured membranes.

## CAUSES OF MORBIDITY

The standard taken for morbidity was a rise in temperature of 100.4°, on any two days after the first day. Table II shows the causes, when determined. In one-third no cause for the temperature rise could be found, and the patients remained

TABLE II. CAUSES OF MORBIDITY

1. Pyclocystitis	6
2. Infected wounds	4
3. Peritonitis	1
4. Culdesac abscess	1
5. Myometritis	2
6. Vesical-abdominal fistula (Latzko)	1
7. Undetermined	7

asymptomatic and made uneventful recoveries. In only 9 of the 22 morbid cases could the temperature be directly traced to the operative field itself.

#### FETAL DEATHS

There occurred 21 fetal deaths, a mortality of 11.8 per cent. However, 4 of these were under seven months gestation, 5 were accompanied by abruptio placentae and dead before operation, and 2 were hydrocephalics which died shortly after birth. In 10 instances or 5.6 per cent were the deaths either unexpected or preventable.

#### MATERNAL DEATHS

Among the 7 fatal cases, four were unexpected, two from peritonitis, one from ether anesthesia, and one from embolism when the patient was ready to go home. In three patients, one in uremia, one in cardiac decompensation, and one with uteroplacental apoplexy and shock which refused to yield to the most energetic measures and repeated transfusions, the outcome was in accordance with the presenting condition. In the uremic and cardiac patients the operation was performed in the interests of the fetus, as maternal death was impending.

Seven deaths in 177 operations gives a mortality rate of 3.9 per cent, or in "corrected" terms, 2.2 per cent.

#### COMMENT

The greatest problem in dealing with patients with contracted pelvis is the management of those primiparas with "borderline" pelvises who rupture membranes before or very early in labor. When the pelvis is generally contracted and the disproportion obvious, the indication is clear. With the membranes intact, an adequate trial is available. But where there is moderate pelvic contraction, or a simple flat pelvis, with early rupture of the membranes, retarded cervical dilatation, and maladaptation of the head, the finest obstetric judgment is needed. The danger in these "borderline" cases is delaying operation until the mother is exhausted and an easy prey to complications, and the baby likely to succumb. Review of the data presented above, showing the past obstetric history and fetal deaths in patients who delivered vaginally at previous parturitions, and consideration of the very high maternal morbidity and fetal mortality (9.5 per cent) in flat pelvis, is convincing evidence of the accuracy of this belief. Unbelievable numbers of women must bear disabling testimony that their vaginal delivery was effected at a terrific price and with a staggering number of fetal deaths.

When patients have previously had cesarean sections, we believe resection advisable, with certain reservations. When the indication for operation does not conflict with possibly normal vaginal delivery, the transverse laparotrachelotomy operation used, and no morbidity traceable to the operative field, a carefully watched trial labor is in order in the subsequent pregnancy. It is no disgrace to section some patients and later deliver them vaginally if the initial indication was just.

The absence of any maternal deaths in 15 placenta previa patients is noteworthy. This is largely due to our prophylactic pre- and post-operative treatment for hemorrhage. By no means do we advise cesarean section as routine treatment for placenta previa. Where a physician lacks special obstetric ability, cesarean section may give better results but that physician has no moral right to handle such a case. Cesarean section should be reserved for selected cases where the judgment of the experienced obstetrician indicates it to be the safer method for the lives concerned.

Our experiences indicate the suitability of cesarean section in certain cases of heart disease and nephritis. These patients should invariably be sterilized if conditions are such that operation is warranted. The results are good. Where the patient's death is inevitable, as in two of our cases, the operation may be used to save the baby without materially hastening the mother's death. In semimoribund cases, it must be done before placental circulation is greatly embarrassed to be of any practical use.

We would comment upon the rarity, in this series, of preeclampsia and eclampsia as indications for section. There were no patients with eclampsia sectioned and only two patients with preeclampsia. Two others had been cleared of preeclamptic symptoms before being sectioned because of flat pelvis. Cesarean section is a highly fatal operation in patients with eclampsia and too dangerous to use, with rare exceptions, in untreated preeclampsia.

In our hands, laparotrachelotomy with transverse cervical segment incision performed under spinal anesthesia is the operation giving best results; lowest mortality and morbidity, fewest fetal deaths, and least number of postoperative symptoms and sequelae. Our experience in this two-year study corroborates that of several preceding years. The Latzko operation finds a definite field in frankly infected cases, with a reasonably low morbidity (20 per cent) and in our 15 cases, no deaths. It may be preferable where an unsuccessful attempt at vaginal delivery has been made. The low classical operation may be preferred by some for placenta previa, or where sterilization is to follow operation, in spite of its definitely higher mortality, morbidity, and dangers if another pregnancy should follow.

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# WHEN TO OPERATE IN RUPTURED ECTOPIC GESTATION\*

## AN ANALYSIS OF 247 CASES

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IN THE "Report on Maternal Mortality in New York City"<sup>1</sup> for the three years 1930 to 1932 inclusive, published by the New York Academy of Medicine, 120 deaths due to ectopic gestation are cited. This group forms 5.9 per cent of the total of 2,041 deaths, a proportion of one to every 16, an astonishingly large number if the number of ectopics encountered is compared with the number of deliveries. From this report the death rate cannot be determined, but in a report by McDonald<sup>2</sup> of a collection of 6,626 cases, all of the patients who were operated upon showed a general mortality rate of 7 per cent. Of the 120 deaths in the Academy report, 91 patients were operated upon and nearly all had symptoms at least a week previously. More than 70 per cent died within five days, indicating, according to the report, "that the shock incident to operation was too great." It is evident, therefore, that reduction in mortality depends upon early diagnosis and proper management.

With these two thoughts in mind, we studied the patients on the service at St. Catherine's and Greenpoint Hospitals, Brooklyn. There are 247 cases in this series. One hundred and twenty have been previously analyzed by Charles A. Gordon.<sup>3</sup> His analysis was conclusive in showing the importance of diagnosis. For the purpose of the record we have added the rest of our cases, numbering 127, noting the diagnostic features of the entire series.

The age of the patients varied from eighteen to forty-two years; 191 or 77 per cent were between the ages of twenty-four and thirty-five. Fifty-three patients had never been pregnant and the longest period of sterility was sixteen years; 73 patients had not been pregnant in five years or more; 194 had been pregnant at least once.

Among the 247 cases there were 8 deaths, a mortality of 3.2 per cent.

The total included primigravida, 53; primipara, 50; multipara, 144, with 2 children 63, 3 children 40, 4 to 11 children 41.

In an effort to determine what may predispose to ectopic gestation we found that 56 had marriage infection as determined by typical history; 112 had previous abortions with several curetted; 49 had dysmenorrhea (premarital); 36 had complicated labor previously; 58 had operations, pelvic and abdominal, as follows: 22 appendicectomy, 2 cholecystectomy, 12 operations for ectopic gestation, 1 suspension of uterus, 2 cholecystectomy and appendicectomy, 1 oophorectomy, 1 "operation on intestines," 1 operation for intestinal obstruction, 2 colpotomy, 1 Dudley operation, 1 operation for umbilical hernia, 6 salpingectomy, 5 laparotomy for sterility, 1 appendicectomy and operation for ectopic gestation.

\*Read at a meeting of the Brooklyn Gynecological Society, October 5, 1934.

The location of the ectopic pregnancy was as follows: right 138, left 107, not stated 2.

	RUPTURED	TUBAL ABORTION	TOTAL
Ampulla	142	72	214
Isthmus	22	--	22
Interstitial	5	--	5
Tubal stump	3	--	3
Not stated	--	--	3
	172	72	247

Vaginal bleeding occurred in 229 cases, and it was marked in 42. As a rule, however, the bleeding appeared as repeated spottings. The average period of amenorrhea was six weeks, a delay of two weeks, but 46 cases missed no period at all. Spotting and pain, however, ushered in the symptoms in every one of these cases. The blood counts were of great assistance in diagnosis and were recorded as follows:

	CASES
White cells: More than 10,000	180
Highest W. B. C. 51,000	
Polys at least 80%	142
Highest polys 95%	
Red cells: Less than 4,000,000	152
Lowest R. B. C. 1,340,000	
Hemoglobin: 50 to 70%	151
Lowest hemoglobin 25%	
Sedimentation time: 18 to 210 minutes	
(60 cases, no constant findings)	

In tabulating the symptoms of which the patient complained we found that 247 had pelvic pain, 123 repeated syncope, 147 vomiting of rupture, 31 passed tissue, 43 painful defecation, 76 painful urination, 36 chill, and 14 had primary pain in shoulder.

In examination of the patient we have noted the following: *Physical Findings:* pelvic mass 197, abdominal mass as well 29, mass indefinite 28, mass not mentioned 10, enlarged uterus 165, soft cervix 121, pain on moving cervix 202, fluid wave 40, shifting dullness 53, breast signs 26, and highest temperature 100° F. 192.

Rigidity, distention, and rebound tenderness were noted in many instances. All three are valuable signs but unfortunately they are often of short duration. They rarely persist. This very fact is, however, of significance in differentiating the diagnosis of ectopic gestation. Rebound tenderness was most persistent, occurring in 25 per cent of our cases.

Preoperative diagnosis was correct in 221 cases or 90 per cent. In 10 cases the preoperative diagnosis was not recorded. Incorrect diagnoses in the remaining 16 cases were as follows: fibromyoma uteri 1, twisted ovarian cyst 1, hydrosalpinx 1, pelvic abscess 1, ovarian cyst 1, fibromyoma with chronic pelvic inflammation 1, post-abortual sepsis 1, and chronic pelvic inflammation 9.

The important features that are of great assistance to us in making an early diagnosis have been presented. However, if we are to reduce the mortality in ectopic gestation, the management of the case will demand both judgment and skill.

Immediate operation is generally considered the proper procedure in the management of ruptured ectopic gestation. To quote Litzenberg,<sup>4</sup> "Even though there be collapse, shock, and alarming blood loss, an operation should be done as promptly as circumstances will

permit," and Schumann<sup>5</sup> says, "All cases of extrauterine pregnancy should be subjected to operation as soon as practicable, regardless of the condition of the patient." Curtis,<sup>6</sup> however, states, "If the patient is in profound shock, temporary delay of intervention is usually advisable." Polak<sup>7</sup> did not favor immediate operation. In his last reference to this question regarding what he called "tragic" cases he stated, "The immediate indication is to combat the shock and control hemorrhage; in an experience of over 400 consecutive ectopics (with a mortality of 2.1 per cent) the writer has done but one immediate operation." It is to this principle, advocated by Polak, that we have adhered in the management of our cases.

For the purpose of discussing this phase of the subject we have divided our 247 cases into two groups as he did—the nontragic and the tragic cases. Of the former there were 167 cases. The problem as to when to operate did not present itself in this group. All these patients were in such a condition that in our judgment they could stand the shock of operation. Either they had had but very little blood loss or were in the reactive stage. They were operated upon after proper preparation.

In the tragic group there were 80 cases. All these patients came to us showing evidence of great blood loss. All were in shock, blood pressure was low, frequently it could not be recorded, and pulse was rapid and of poor quality, often imperceptible. The body surface in many of these patients was cold and clammy. The blood picture and clinical appearance of the patient, in every instance, indicated profuse hemorrhage.

It is with this latter group of 80 tragic cases that we are concerned in our discussion of when to operate. The problem would not have presented itself in the majority of these cases if diagnosis had been made when symptoms first appeared. In 59 instances there was a clear history of previous, and often repeated, rupture, and the average time elapsing before the patient entered the hospital after the rupture that produced the tragic picture was eighteen hours.

It was our judgment that patients in the tragic group were not fit to stand operation. We felt that the added shock incident to operation would be too great and our patients could not survive. With this as our problem our efforts were devoted to combating the shock.

The treatment at this time consisted of absolute rest, ward screen, shock position, complete morphine immobilization, one-fourth to one-half grain on admission, often a fourth within the hour and another fourth every three or four hours, external heat, no stimulation, no enema. We have found hypodermoclysis with Ringer's solution very valuable and, on account of its slow absorption, not at all contraindicated. Blood transfusion played an important rôle; however, in many instances this measure was not resorted to, improvement taking place

to our satisfaction without it. We feel that in spite of the most careful typing and cross matching of bloods, transfusion is not without risk. (One of our fatal cases we classified as a blood transfusion death.) This does not mean that this measure is not a valuable and life-saving procedure in the management of ruptured ectopic gestation, but it is not the panacea that some would have us believe, nor does it in any way guarantee a successful operation. More than 50 of our patients improved without it, so as to be satisfactory subjects for operation.

Notable reaction occurred usually within a few hours: our efforts were rewarded in 75 instances in the 80 cases. The improvement was such, that in our judgment, operation could be performed without undue risk to the patient. In 5 cases improvement was not noted. It is our policy to institute treatment to combat shock in all tragic cases. Blood pressure is frequently taken (the cuff constantly remaining on the arm), the pulse repeatedly recorded, frequent blood counts taken, and the general condition of the patient constantly observed. Failing to react, operation is performed anyhow. However, it is only in very rare instances that such an occasion arises.

When the patient has reacted to the point where she will in our judgment stand the operation, it is performed. Further delay has its dangers, too, in that rupture may again take place, and hemorrhage recur. Operating when the systolic blood pressure is between 90 and 110 has proved a safeguard for us against this catastrophe.

Operations were performed by 8 operators. The skill of the surgeon should be, and is, an influence when the decision as to when to operate is to be made. Crossen<sup>8</sup> states: "In these cases immediate abdominal section is advisable as a rule, if the patient is within reach of an experienced abdominal surgeon and can be placed in suitable surroundings. In the absence of an experienced operator and suitable facilities, operation had best be deferred." It is obvious that the expert may, with comparative safety, operate upon patients in varying degrees of shock. However, the casual operator cannot expect good results in such cases. Many tragic cases will fall into the hands of the unskilled, and to our minds best results are to be obtained if shock is first combated.

That ruptured ectopic gestation calls for surgical intervention is clear. That operation should be done at once is generally held. It would seem that the patient is suffering from progressive hemorrhage, is bleeding to death, and the bleeding vessel must be ligated. That active bleeding is not often encountered at operation even in our most tragic cases is evident in our series. Only six times was it noted, and then it is reasonable to assume that pelvic exploration, or even opening of the abdomen itself, may have caused it. Halliburton and McDowall<sup>9</sup> state: "Unless a large vessel is opened hemorrhage is for

various reasons seldom fatal. The damaged blood vessel retracts and contracts and this, together with the clotting of the blood, tends to close the opening while the formation of a clot is facilitated by the fall of arterial pressure. For these reasons, section even of such a large vessel as the radial artery may not cause death."

Seventy-six of the patients in our 80 tragic cases were operated upon and the operative procedures are noted in Table I.

TABLE I

REMOVAL OF	ALL CASES	TRAGIC CASES
One tube	140	53
One tube and ovary	91	23
Both tubes	6	0
Uterus	5	0
Ovum from tube and resuture	1	0
Appendix also	5	0
No operation	4	4

No anomalies were noted, although examination of torn and distorted material is very difficult.

The appendix was removed in 5 cases of the nontragic group. This certainly should not be done, nor should any other operative procedure accompany that which is done for ruptured ectopic, with the abdomen filled with blood.

In all but one tragic case correct diagnosis was made, and this without culdesac puncture; which we consider unnecessary and perhaps dangerous. All patients presented a large amount of blood in the abdominal cavity, and only the large clots were removed. There was no drainage in any case.

The location of the pregnancy was as follows: ampulla 52, isthmus 19, interstitial portion 4, fimbrial end 2, and not determined 3.

In this series of 247 cases there were 8 deaths, a mortality of 3.2 per cent. Briefly the details of these deaths were as follows:

1. In profound shock on admission. Had curettage for pain and bleeding two weeks before admission. Died six hours after admission. This patient failed to show any improvement whatever. Was never fit for operation. Autopsy showed extensive rupture in the isthmus.

2. Admitted with imperceptible pulse, blood pressure 0, cold and clammy skin. Died four hours later. Absolutely no improvement and never in condition to be operated upon. Had sought relief for pain, vomiting, and bleeding one week before, and condition diagnosed as threatened abortion by family physician. No operation, no autopsy, but included in this series because our diagnosis was ruptured ectopic gestation.

3. Died five minutes after admission. History of rupture eight hours before. Autopsy, rupture of interstitial portion of tube.

4. In shock on admission. Condition remained unchanged but operation was performed anyway, after delay of eighteen hours. Rupture of tube at isthmus. No active bleeding. Died eleven hours later. Death due to shock. Two days before admission attended by family physician, and again day before admission. Refused advice to enter hospital until what was probably a third rupture occurred.



5. Admitted with diagnosis of postabortal sepsis. Cured ten days before admission to induce abortion. Admission diagnosis of septic abortion made; not seen by attending staff. Expired three hours after admission.

6. In shock; responded to supportive treatment, operated upon and died twenty-four hours later of acute sepsis. Family physician prescribed for pain and bleeding two days before admission.

7. In shock on admission. Reacted to supportive treatment, operated upon, died twenty-four hours later of acute sepsis. History of rupture eighteen hours before admission.

8. Admitted in shock. Operation after reaction. Bleeding controlled. Blood transfusion given while patient was still on operating table following operation. After 180 c.c. were given sudden unexpected death. Clear history of rupture two days before admission.

From the above it will be noted that 5 patients did not improve under treatment. Only one was operated upon, and eleven hours later she died of shock. Of the patients who did not improve one was in the hospital only five minutes, one three hours, one four hours, and one eighteen hours. In this last case the fact that the patient was not improving was not appreciated. In one case the diagnosis was not made.

Of the patients that did improve, one died after a transfusion and two died of sepsis.

Four of these patients were not operated upon. In the 243 patients that were operated upon there were 4 deaths or an operative mortality of 1.7 per cent.

In all there was a definite history of rupture from eight hours to two weeks before admission and 5 of the 8 patients had been treated at home for symptoms indicating rupture.

#### SUMMARY

1. In this series of 247 cases of ruptured ectopic pregnancy diagnosis was not difficult; pain and bleeding were present at some time in every case.

2. Eighty cases or 32 per cent were in shock on admission, and operation was delayed. In all but 5 of these 80 cases shock was combated successfully, and 75 cases or 94 per cent improved sufficiently to withstand the added shock of operation.

3. The total mortality of 8 or 3.2 per cent might have been less if transfusion had always been as quickly obtained as it is today.

4. There is no evidence to show that this mortality would have been any lower if immediate operation had been done. On the contrary we feel that such a policy would have increased the risk for all these tragic cases.

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## THE MANAGEMENT OF PROLAPSE OF THE UTERUS\*

WITH ESPECIAL REFERENCE TO THE MANCHESTER-FOTHERGILL OPERATION

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IN MAY, 1933, W. Fletcher Shaw presented to the American Gynecological Society a paper on "The Treatment of Prolapsus Uteri, with Special Reference to the Manchester Operation of Colporrhaphy." He reported 549 cases with 96.3 per cent free from recurrence, slight morbidity and no mortality; he sees no reason why anyone should do any other operation, or why prolapse should be divided into different types for various operations. For forty-five years, according to Shaw, this operation has been done by a large number of gynecologists in Manchester on all patients with prolapse, irrespective of age, social position, or parity, and "the results allow more nearly a guarantee of cures . . . than does any other operation in surgery." W. E. Fothergill, by whose name the operation is best known to us because of his very practical modification of Donald's original technic, has published equally good results. Alfred Gough in 300 Fothergill operations found it perfectly adequate in 95 per cent of his cases, so satisfactory that he hardly dared modify it; he states that this operation is practiced by a large proportion of British gynecologists.

At the same time this operation has not found favor here, although it is known to many, and particularly to those who have seen it done in Manchester. Maier and Thudium, however, have reported 138 cases with cure in 111 out of 113 followed up, or 98 per cent; of 47 in the childbearing age, 11 patients had 13 children, with 10 normal deliveries. In Fothergill's cases, 26 had 30 children subsequently, 27 normally, while in Shaw's series, 27 had children, 5 with recurrence of prolapse.

Anatomic discussions needlessly complicate the subject. No doubt there are many factors involved in maintenance of the uterus at its normal level in the pelvis; the structures of the pelvic outlet must be interdependent. Mackenrodt's description of the cervical attachment of the strong connective tissue sheaths of the uterine vessels has not been universally accepted, although the Manchester-Fothergill operation aims to shorten this supporting tissue. Bissel's investigations, according to Goff, have convinced him of the importance of the visceral portion of the endopelvic fascia beneath the uterine vessels in the bases of the broad ligaments, the so-called cardinal ligaments of the

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\*Read at a meeting of the Brooklyn Gynecological Society, October 5, 1934.

uterus; the posterior cervical part of this same fascia also aids, while the vesicovaginal fascia, he thinks, is areolar and too weak for much support. Nyulasy shows illustrations and Spalding photographs of these cardinal ligaments, yet Koster has not been able to find them. An important part of the Halban operation is the reefing of the very vesicovaginal fascia which Goff has found to be so frail; not dissectable as a distinct layer according to Goff, Spalding found it to be 1.5 cm. thick, and Halban maintains that it can be found and dissected free in every instance. It should be observed, however, that none of the gross dissections or microscopic studies of Spalding, Sears, Goff, or Koster was made on a patient with prolapse, whereas it is our experience that in such patients the transverse cervical ligaments are much lengthened and hypertrophied and contain muscular tissue which probably originated from the uterus. It is obvious, too, that no uterus could descend without elongation of the parametrial supporting tissue, whatever name we may give it, and there is no reason why compensatory hypertrophy may not follow great elongation of this tissue; in other words, its density may increase with the functional demands upon it.

That the peritoneal ligaments of the uterus are unfortunately named and of little value for support is obvious. The importance of the levator ani is a subject for discussion. Because we have seen great stretching of the vaginal tube with rolling out of its walls, deep forceps laceration of the lateral vaginal sulci, and because complete tears of the perineal body into the rectum are rarely associated with prolapse of uterus, and never cause it, we have felt that levator fascial repair was of little importance. Since we see severe lacerations without prolapse, and prolapse without lacerations, one cannot cause the other. We have rebuilt the posterior wall only to narrow the vagina, change its direction, lengthen it when possible and place beneath the uterus firm tissue which would at least make descent difficult and tedious. Rectocele precedes prolapse and has nothing to do with it.

At St. Catherine's Hospital the Department of Obstetrics and Gynecology has elected the Manchester-Fothergill operation for prolapse since 1917. Then we thought that hysterectomy was the worst operation one could do for prolapse, yet it is obvious that prolapse may be cured that way. The Mayo-Goffe operation was done only when intrinsic pathology warranted removal of the uterus. In no case was relief of prolapse attempted by abdominal operation alone. A combined operation has been done for associated intraabdominal lesions, and five of our early Fothergill operations, the last in 1928, were subjected to some form of intraabdominal shortening of the round ligaments. That was unnecessary. Interposition we have always thought limited in its application and of doubtful expediency. No other operations have been done.

We have reviewed 170 consecutive cases of prolapse of the uterus admitted to St. Catherine's Hospital from 1917 to 1933. No case is included where the cervix did not descend at least halfway down the vagina, and no case of cystocele without similar descent. Grouping cases according to the degree of prolapse would be valuable, but there is no generally accepted classification. To some "third degree" or "complete" means protrusion of the cervix, and we found many cases in our records were so designated. It is clear, however, that complete prolapse should refer only to protrusion of the entire uterus, so I have found it more practical and informative to divide the cases into (1) protrusion of the entire uterus, (2) protrusion of part of the uterus and (3) descent at least half down the vagina, without protrusion.

TABLE I. DEGREE OF PROTRUSION

AGE	ENTIRE UTERUS	PART OF UTERUS	NO PROTRUSION	TOTAL
20-30	—	2	8	10
30-40	6	16	30	52
40-50	6	21	30	57
50-60	14	16	9	39
60-70	8	1	—	9
70-80	2	1	—	3
	36	57	77	170

The fundus was absent in one case of protrusion of the cervix with complete inversion of the vagina. Enterocoele was recorded in only four cases, but I think that its recognition is not easy unless well established. Cystocele and rectocele occurred with prolapse in 142 cases; the absence of rectocele was noted in 28 cases. The fundus cannot descend without carrying the bladder with it, but the cervix, by hypertrophy of its supra- or infravaginal portion or both, may protrude with or without cystocele or rectocele, in one case without cystocele the long thin portio was found four inches beyond the vulva. Elongation of the cervix occurs very frequently with prolapse, but it also occurs without it. The cause of this lesion is unknown. Anatomically it is not prolapse, but clinically it is. Those cases listed as hypertrophy of the cervix with protrusion, and inversion of the vagina from above downward, not everted from below upward as in classical prolapse, are tabulated in Table II.

TABLE II. PROTRUSION OF LONG CERVIX

Without cystocele or rectocele	4
With cystocele only	12
With rectocele only	4

The obstetric history is interesting chiefly because in 121 cases, or 71 per cent, there had been no instrumental or operative delivery. Tabulations are shown in Table III.

The most common symptoms were urinary: urgency, frequency, incontinence, nocturia, tenesmus, burning and inability to void without replacing the prolapsed mass; discharge, menorrhagia, postmenstrual bleeding, bearing down, protrusion, pelvic pain, dysmenorrhea, rectal tenesmus and backache were other symptoms recorded. Backache is a classical symptom of prolapse, yet many women did not complain of it, and for that matter, some did not complain of protrusion either, although it was

TABLE III. OBSTETRIC HISTORY

Spontaneous		121
No. of children	{ 1 only	12
	{ 2-14	109
Instrumental		40
No. of children	{ 1 only	10
	{ 2-7, first instrumental	9
	{ 2-7, one or more instrumental	10
	{ 2-11, all instrumental	11
Not stated		9

considerable. There is no constant symptom, and symptoms are of no importance as aids to diagnosis; they should be recorded, however, as complaints for which the patient seeks relief.

TABLE IV. OPERATIONS FOR PROLAPSE

Watkin's interposition	4
Mayo-Goffe vaginal hysterectomy	14
Manchester-Fothergill	152
Manchester-Fothergill with round ligament operations	5
Manchester-Fothergill with other procedures	14
	<hr/> 170

The Watkins operation was done four times, all on patients in the fifth decade. Large cystocele was the indication. The last operation was done in 1929. The Mayo-Goffe operation was done 14 times. The youngest patient was forty-one, the oldest sixty-seven. In the two cases before the menopause, the hysterectomy was done for adenomyosis in one case, dysmenorrhea in the other. In the other 12 cases, hysterectomy was done for postmenopausal bleeding (8), possible malignancy of the cervix (3), and fibroid (1). In no case was malignancy found by the pathologist. One patient had a pulmonary embolism. All recovered.

The Manchester-Fothergill operation was performed in 152 cases, in 50 of these without amputation of the cervix. So far as possible we have cauterized or occasionally repaired the cervix of young women because we fear that amputation may later cause abortion. In no case, however, have we left a measured uterine depth of more than three inches. In all cases high posterior colporrhaphy was done. Description of the operative technic is unnecessary, as we have modified Fothergill's very little, taking care only to use Halban's sphincter stitches in patients with urinary incontinence. Interrupted chromic gut No. 2 was used throughout, with No. 1 for subcuticular skin closure. Diagnostic curettage was not done routinely. Denudations were as wide as possible and then trimmed, as it is best to overcorrect vaginal slack. Preoperative preparation consists of rest in bed until ulcers and swelling are relieved; obviously it is safer to await healing of cervical ulcers, but where time presses the actual cautery may be used at operation. Postoperative care is simple; no douches, occasional gentle irrigations with boric acid solution with a glass catheter and a syringe, glycerin enema on the fourth day.

Other operative procedures were combined with vaginal plastic surgery in 19 cases; hemorrhoidectomy (1), intrauterine insertion of radium (2), vaginal myomectomy (1), abdominal myomectomy (1), appendectomy (2), inguinal hernioplasty (1),

appendicectomy and cholecystectomy (1), salpingo-oophorectomy (2), shortening of round ligaments (5), and supracervical hysterectomy (3). The last three cases need further explanation. One was for a large myoma, and the other two for bleeding associated with pelvic pain. In every case a heavy ring of cervical tissue was preserved at the level of the internal os.

It will be observed that, except for the occasional incidence of fibroid or adenomyosis, patients with prolapse are singularly free from other pelvic pathology. In no case was malignancy of the corpus present. Cancer of the cervix was not found by the pathologist in the four cases in which its presence was suspected; these cases had vaginal hysterectomy without previous biopsy. In one plastic, however, with amputation of the cervix, a diagnosis of cervical carcinoma was made on the tissue, and radium was placed in the cervical stump twelve days later; this patient has remained well three years without recurrence. Chronic pelvic inflammation, so common otherwise, was not seen nor was its presence suspected in any case. Diabetes was present in four cases. Many patients were not good risks, and a few early operations were done in two stages. No one was rejected for age. One patient with complete prolapse, myositis ossificans and ankylosis of both hips was satisfactorily operated upon although the approach was difficult.

Anesthesia was gas-oxygen-ether or ethylene in 158 cases; two were done under spinal novocaine, and in 10 cases, 8 Fothergill and 2 Mayo, local anesthesia was used, injecting first the perineum and labia, then the sulci and parametria; the anterior wall itself rarely required infiltration. Of late years all patients are given 9 gr. of luminal or 10 gr. of veronal with  $\frac{1}{4}$  gr. of morphine or  $\frac{1}{150}$  gr. of scopolamine before operation. This preliminary medication is essential to the success of local anesthesia, which is now routine for all cases and perfectly satisfactory. Now poor risks are not rejected.

#### MORTALITY AND MORBIDITY

There were two deaths in this series, one from bacteremia ten days after the vaginal plastic, the other from pelvic thrombophlebitis. This last was a two-stage operation. Although the record is not clear, I suspect that peritoneal sepsis followed repair of enterocele. This 1 per cent mortality is high for vaginal plastic surgery. Although Shaw has reported 549 cases with no deaths, he has had nine deaths in twenty-six years. We should expect no mortality from the Fothergill operation.

Slight bleeding about the sixth or seventh day is not uncommon after the Fothergill operation, nor is foul discharge. Two patients bled severely on the sixth day and one was lightly packed; this was probably due to infection and sloughing. Eight cases were complicated by pelvic cellulitis with the peritoneal rebound and low abdominal tenderness of parametritis. Two had phlebitis. Two had pulmonary embolism, one after Mayo, the other after Fothergill; both recovered. One had psychosis, another a strangulated hemorrhoid due to a suture, and another cellulitis of the arm due to hypodermic injection. No other complications were recorded. All the other patients recovered nicely, and were allowed out of bed on the fourteenth day.

## END-RESULTS

All these operations were performed by four operators. In 94 cases follow-up has been sufficiently close and personal to warrant a report on the end-results of the Manchester-Fothergill operation, since all of these were private patients operated upon by me and observed at intervals for at least two years, many for three years and some for as long as thirteen years.

In every case prolapse of the uterus was cured and the uterus found at a level high enough to cause no symptoms of bearing down or weight. However, one patient, aged forty-nine, with a history of seven operations for prolapse over a period of thirty years, complained, within six months, of recurrence of all her symptoms of dragging, pelvic pain on standing or walking, urinary frequency and vaginal fullness; cystocele had recurred, but the cervix was high and fixed with dense scar tissue about it. In two cases large enterocele recurred within three months of operation; repair was satisfactory. In three cases cervical stricture caused hematometra, relieved by dilatation. It had not been our practice to thoroughly dilate the cervical canal at the time of operation, as advised by Shaw and Fothergill; this should prevent this complication. In nine cases urinary symptoms still persisted; in none of these, however, was secondary anterior wall repair thought necessary, although in six cases moderate cystocele was present. If we consider urinary symptoms, slight cystocele and hematometra minor defects, and enterocele or large cystocele evidence of failure, 91 cases were satisfactory results or 96.8 per cent.

In this group of 94 patients, 22 were in the childbearing age. Four have had one baby since the operation, and two have been delivered twice; in one of these when the rigid cervix was cut, delivery was prompt and spontaneous; her next delivery was easy. In all these cases the perineum was cut or torn, but prolapse did not recur. One patient had two abortions, each in the third month, doubtless due to amputation of the cervix.

## CONCLUSION

It has been clearly shown by many operators that even the worst types of prolapse of the uterus may be cured by vaginal plastic surgery. No abdominal operation then should be done for prolapse. Since the parametria may be united in the midline without removal of the uterus, why remove it? Hysterectomy should be reserved for those patients in whom the uterus is diseased; removal of the normal uterus for the cure of prolapse is unnecessary, and in young women wrong. The Manchester-Fothergill is all that could be desired, and it should have no mortality. That it does not interfere with parturition may not perhaps be proved, but many women have been successfully and easily delivered after operation. Reviewing our results after

seventeen years' experience with this operation, we are satisfied that it accomplishes the most with the least risk, and that has always been a good rule in surgery.

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## TWO YEARS' EXPERIENCE WITH THEELIN TREATMENT OF GONORRHEAL VAGINITIS\*

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TREATMENT of gonorrheal vaginitis by the use of female sex hormones first suggested by Dr. Robert M. Lewis<sup>1</sup> opened up an interesting new field in therapeutics, namely, the use of hormones to alter tissues in such a way as to combat infection.

In a recent study, Jungblut and Engle<sup>2</sup> attempted to reproduce in immature monkeys a state of mature insusceptibility to the virus of poliomyelitis. They showed that immature monkeys prepared with glandular anterior pituitary hormones and anterior pituitary-like principles from the urine of pregnant women are protected only in exceptional instances against intercerebral infection with poliomyelitis virus. However, the serum of such prepared animals frequently acquires the property of inactivating the virus in vitro.

Lewis quite properly approached the subject of this hormone treatment conservatively, cautioning against possible dangers of the treatment, and subsequent articles by Brown<sup>3</sup> and by Haberman and Israeloff<sup>4</sup> have also been encouraging but cautious. The apparent simplicity of this treatment and its favorable preliminary reports might, however, lead to the hasty conclusion that a lasting cure is easily obtained.

Fundamental questions present themselves: (1) Does arrest or cure take place and, if so, how often and how permanently? (2) Are there any deleterious effects on the children?

\*Read at a meeting of the New York Obstetrical Society, October 9, 1934.

NOTE: For lack of space the extended tabulations of cases could not be included. These may be found in the author's reprints.



The answer to the first question cannot be made in a definite manner, as yet, nor can we answer the second question except to say that, so far, no bad effects have been noted. It seems desirable, therefore, to present further experience with this treatment and to caution that it is still in the experimental stage.

The present series of sixty-eight cases was studied in the Hartford Municipal Hospital, and its Out-Patient Department, with the exception of the last five, whose records were furnished by the courtesy of Dr. Louis F. Middlebrook who has studied them at the Hartford Dispensary. This latter clinic has also cooperated in part of the care of many of our other patients.

With the exception of the first few cases the hormones used have been purchased in the open market. The necessity for economy in spending the city's money has led us perhaps to underdosage as will be seen in reviewing the protocol summaries. The hormones used were Parke, Davis & Co.'s theelin and theelin in oil, given intramuscularly, and theelol capsules, by mouth, G. W. Carnrick Co.'s thelestrin, intramuscularly, E. R. Squibb & Sons' amniotin in oil, given by mouth. (Where amniotin is mentioned in the protocol the oral product is indicated.)

In order to obtain a bird's-eye view of the effect of treatment from week to week, a special chart was used. We have used the well-known gradation of 1-4, in which 4 is the largest amount observed and 1 is the smallest, 0 being absent. Such a system is, of course, not absolutely quantitative, but in a general way, if done by the same observer, it is better than the use of descriptive terms.

We have estimated the amount of vulvovaginal irritation, discharge, and the intensity of the theelin reaction, as described by Lewis. All smears were taken with a wire loop, using the knee-chest position in the older children. We have noted the amount of vaginal material obtained and its appearance before drying as it is spread on the slide, for we have noticed that when squamous cells were numerous the fresh smear has a translucent or glassy appearance as contrasted to the muddy or opaque appearance when white blood cells are numerous.

On the microscopic examination we have noted the presence of intracellular or extracellular organisms, Gram stain being used throughout, and have tried to estimate the relative number of white blood cells and squamous cells.

The bacteriologic work was done in the Hartford Board of Health laboratory as part of its routine work, and it is too much to expect that these quantitative estimates can be taken too seriously. We believe, however, that the careful study of the smear can replace the vaginal wall biopsy as a control of the theelin reaction.

Eight mothers of 12 children were known to have had active gonorrhea, seventeen of the children had one or more sisters who were infected, and in 3 instances, at least, contact infection from a sister seems to have been highly probable. In the absence of cultural studies, however, we can question whether every case was a true gonococcal infection, for upper respiratory infections and the exanthemes seemed to complicate the onset, or to bring about relapses after a child had been bacteriologically free for as long as six months.

Many complicating diseases occurred during the treatment of these children. Ophthalmia was seen twice and was treated independently, having apparently no effect on the vaginal infection. Proctitis was found once and was quickly cured following potassium permanganate rectal irrigations.

Urethritis was seen 6 times, usually in cases which tended to recur repeatedly. This complication, undoubtedly, was present for a time in others. The urethra apparently is uninfluenced by the hormone, for the reaction, especially in the negro children, can be seen to limit itself quite distinctly to the muellerian tissue, ending at the hymen. No local treatment was attempted for urethritis. Perhaps a ketogenic diet rendering the urine acid would be as effective as anything.

Salpingitis was seen only once in a young child, aged five, and twice in older children aged ten and eleven years, respectively. This infection regressed rapidly under simple bed rest.

Puberty reactions were observed in 3 children at ages nine, ten and eleven years, some months after treatment. These children were of Irish, Swedish, and German parentage, respectively. Swelling of the breasts was not observed in any of the younger children even under prolonged treatment.

A few of the cases, it will be noted, remained negative following treatment which seems to have been obviously insufficient, but we are reporting every case irrespective of the results. We feel that other defense mechanisms than the hormones have been at work, and it may well be that all we can do with the hormone reaction is to clear the vagina and keep it clear while the natural immunity reactions develop and while infections in the urethra clear up independently.

It was noted that fresh infections required much longer treatment than did old infections, again emphasizing the part that immunity may play.

A few interesting cases are given in more detail, as follows:

CASE 1.—E. S., admitted at age of six months with congenital syphilis and gonorrheal vaginitis. She was hospitalized as an orphan for nearly three years and left for adoption apparently cured of both diseases, in spite of many months of serious complications including otitis and bronchopneumonia. This child started theelin treatment as reported by Dr. Lewis, receiving 50 R. U. daily for fifteen days. A

relapse was treated again similarly with a total of 2,050 R. U. The smears became negative and have remained so for fifteen months when last examined.

CASE 2.—M. S., aged five years, admitted with lobar pneumonia and gonorrheal vaginitis. During her admission for pneumonia she was treated with the usual antiseptics and discharged after 10 negative smears only to have the vaginitis recur in three months. As reported by Dr. Lewis she was given 50 theelin R. U. for fifteen days. The vaginitis cleared promptly and the patient has been entirely negative except for a few extracellular organisms two and four months after treatment. Observed twenty-three months at last examination.

CASE 3.—M. Y. This patient was aged four days when first admitted as a feeding case. She was discharged and readmitted at age of three months with gonorrheal vaginitis, receiving local antiseptic treatments. At a third admission for recurrence she was treated with antiseptics for five months without results, and as reported by Dr. Lewis, theelin was then given, 50 R. U. for fifteen days. The vaginitis promptly cleared and she remained negative for two years. She was fifteen months of age when treatment was started. Unfortunately she showed a positive smear at her last examination, and we may fairly ask (1) whether this is a true recurrence, (2) whether it is a new gonorrhea, or (3) whether it is an infection simulating gonorrhea. Such cases show that the word "cure" must be discarded, and we must be more exacting in our follow-up requirements.

CASE 4.—M. B., an orphan, aged three years, acquired gonorrheal vaginitis evidently from her sister. She had been negative on daily smears three months previously when examined as a contact. This patient had one of the most extensive and persistent infections which we have seen, involving not only the vagina but urethra and rectum, with many condylomas surrounding the vulva and anus. She did, however, escape salpingitis. The child was studied also by biopsies and received theelin, 50 R. U. daily, or twice 25 R. U. Later theelol by mouth was tried, 50 R. U. with fairly good reactions. Amniotin in oil, 30 R. U. 3 times daily, by mouth, was tried for fifty-two days without noticeable effect. Thelestrin, at first, gave good reaction in doses of 25 R. U. twice daily, but a later shipment failed to give a good reaction in twice that dosage. She has always responded quickly with an intense vaginal proliferation when enough rat units were supplied. We are now trying to keep up a moderate reaction for three months to see if we can wear out the infection. The proctitis was treated by permanganate irrigations and cleared quickly. To summarize her treatment which has now lasted twenty-three months, she has had 20 series of hormone injections and 14 times has shown a more or less vigorous vaginal reaction. She has never shown tenderness of the breasts, and has developed into a sturdy, apparently healthy child, but the end is not yet in sight for she has just shown one more recurrence while under treatment.

CASE 5.—P. D., aged eight years, admitted with otitis media and gonorrheal vaginitis. She was started on amniotin in oil, by mouth, 30 R. U. twice daily, later increasing to 60 R. U. twice daily, and when no reaction was obtained we increased to 300 R. U. twice daily. A total of 19,230 R. U. was given, of which 12,900 R. U. had been recently standardized for us by Edgar Allen of Yale University. The three biopsies of the vaginal wall at weekly intervals showed no appreciable change during this oral administration and her smears remained positive. Under three series of injections of thelestrin, 50 R. U. daily, totaling 600, 400, and 600 R. U., respectively, the infection cleared up and she remained negative for five months when last seen. During June of this year, two months after stopping treatment, I noted beginning swelling of the breasts, and during July a well-developed "theelin reaction" of the vagina was seen, although no treatment had been given for over two

months, and she had shown the usual involution of vaginal epithelium subsequent to her last treatment. She is now nine and one-half years old, and it is possible that this reaction constitutes the first sign of approaching puberty. Whether or not it was hastened by the treatment remains a question.

CASE 6.—H. R., aged four years, admitted for gonorrheal vaginitis and started on theelol, by mouth, 25 R. U. 3 times daily. Three biopsies were taken at weekly intervals and showed a moderate reaction. Smears became negative after 3,175 R. U. were given but were positive again within a month. The second series of theelol, totaling 1,000 R. U., was given with a better reaction but prompt recurrence of the infection. A third series of 1,000 R. U. was given, 50 units twice daily, likewise a fourth series of 700 R. U. Theelin was then given hypodermically, 25 R. U. twice daily, totaling 1,350 R. U. A fifth series of 600 R. U. of thelestrin was given, and a sixth series of 550 R. U. was given. A seventh series of 1,800 R. U. of theelin in oil was given hypodermically, 300 R. U. daily, and an eighth series of the same dosage was given. Gonococci were last seen in the smear preceding the last series in June, 1934, and we are trying here also to keep up a vigorous reaction over several months, since this child relapses easily if treatment is intermittent.

Perhaps as an anticlimax we may mention the case "L. C.," a newborn baby delivered in another hospital of a mother who had gonorrhea. The child quickly developed a gonorrheal ophthalmia and vaginitis and was started on theelin, 25 units twice daily for 22 doses before being admitted to the Municipal Hospital. She was under constant observation in our clinic until, at the age of four months, she left town. This child, beginning at the tenth day of life, had almost constant daily injections of 50 units, receiving in all 3,250 R. U. The theelin reaction of the vagina was constantly present but pus cells and the gonococcus did not disappear in the smears during three and one-half months of treatment. Fortunately, we were able to have this child brought back for follow-up examination just one year after birth, at which time she was clinically and bacteriologically free from any sign of infection. It is only fair to state that the theelin treatment may have had a beneficial effect, though it is disappointing not to have seen the infection clear up while under treatment. Clinical improvement, however, was marked, and we had expected the gonococci to disappear in a short time of additional treatment when the child was removed from our care.

#### CONCLUSIONS

1. Gonorrheal vaginitis may be cleared up more or less promptly in many cases following the establishment of a female sex hormone reaction, as described by Lewis.

2. Relapses are frequently due to reinfection from the urethra, and will be found more frequently if long-continued follow-up studies are made.

3. Acute recent infections require longer treatment and larger doses than long-standing infections.

4. One of the first signs of approaching puberty appears to be a vaginal epithelial proliferation which cannot be distinguished from the hormone reaction described by Lewis.

5. We have gained the impression that the vaginal infection, whether it is due to a gonococcus or other organism, responds equally well to the treatment.

6. We suggest tentatively as a plan of treatment that the child be cleared as rapidly as possible with daily injections of at least 100 R. U., preferably in divided doses, diminishing the amount as a reaction is obtained but maintaining a vigorous squamous cell reaction until the gonococcus disappears, and thereafter maintaining over a period of two or three months a moderately well-developed reaction, during which time the child may be allowed to go to school, subject to weekly observation by smears.\*

7. We cannot say that this treatment is harmless, for we do not know what it is doing to the ovaries, and we await with curiosity the opportunity to inspect the ovaries at operation. So far, at least, deleterious effects have not been manifest.†

8. We have presented a study of female sex hormone treatment of 68 cases of gonorrheal vaginitis of which 42 have been observed for six months or longer. Twenty-three of these have been observed for one year or longer.

9. End-results of these 42 cases may be given in terms of negative smears for the time stated, and in which the result apparently had some relationship to the treatment, as follows: Good results, 19; temporary control only (up to the present time), 16; frank failures, either due to insufficiency of dosage or lack of cooperation, 7; 26 cases studied less than six months are not included in this summary. Further subdivided, the results may be given as follows:

Over one year:		Six months to one year:	
Good	6	Good	13
Temporary	12	Temporary	4
Unsatisfactory	5	Unsatisfactory	2

We wish to express our thanks to Dr. Robert M. Lewis for allowing us to participate in this interesting research, and for his many helpful suggestions during the course of the study.

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\*An excellent study of the social significance of gonorrheal vaginitis as it affects the schools is contributed by Ella Oppenheimer and Roy H. Everett in the J. Social Hyg. 22: 129, 1934.

†Recently this opportunity presented itself during an operation for appendicitis on a nine-year-old child who had received 50 units of thelestrin twice daily for ten days. Vaginal clippings showed a typical Lewis reaction. Biopsy of the ovary showed no reaction.

## CESAREAN SECTION AND ITS ABUSES\*

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IN THE past decade we have witnessed a great increase in the incidence of cesarean section in this country. Unfortunately this rise in the number of operative deliveries has not been accompanied by a corresponding decline in mortality, either maternal or fetal, but on the contrary, by a higher death rate. Truly a sad state of affairs. A questionnaire sent to hospitals in this country by the White House Conference brought to light incidences of cesarean section as high as 14.6 per cent in some hospitals. Plass found the incidence in the southwestern states to be highest when compared with other sections of the country. It is worthy of note that although one sees great differences in the incidence of cesarean section in foreign clinics, one fails to observe there the excessively high rates as seen in some of our American institutions.

We would not be so concerned over the incidence of cesarean section were it not for the fact that this operation, as done throughout the country, carries with it a maternal mortality close to 10 per cent. Large series of cases have been reported from different sections of the country, carrying with them maternal mortality rates ranging from 1.7 to 16.1 per cent. In 1927 Davis reported a figure for this city of 14.4 per cent.

It needs no argument on my part to convince you that such results cannot and should not be tolerated. At last the lay public is waking up and asking our profession: Why this sacrifice in mothers? This steadily increasing tendency to effect delivery by operative means, mainly on the part of the improperly trained and unskilled, but sometimes also on the part of those who should and do know better, has been a great factor in keeping our maternal mortality rate in the neighborhood of 7 to 9 per 1,000 live births. The improvement that may be effected in a few scattered areas is more than offset by this ever rising tide of unnecessary operative deliveries with their frightful death rates.

Plass in his excellent statistical study of this question stated that a conservative estimate of the maternal death rate in cesarean section in this country is between 5 and 10 per cent and probably nearer

\*Read before the Post Graduate Medical Assembly of South Texas, Houston, Texas, October 3, 1934.

the latter figure. He estimated that 25,000 cesarean sections are done each year in this country, which would mean a death list of 2,500 mothers a year. Three-fourths of these sections are undoubtedly unnecessary, in other words close to 2,000 women are unnecessarily sacrificed each year due to this urge to operate. I agree with Plass when he states that "a diminished cesarean section incidence would result in bringing our national maternal death rate down more nearly to that of other countries where vaginal delivery is more common and where the physiologic character of labor is better appreciated."

I shall present the statistics on cesarean section for the Woman's Clinic of the New York Hospital. They cover a period of two years, from Sept. 1, 1932, when the hospital was opened, up to the present time. During that period we had 5,456 deliveries in the hospital with 153 cesarean sections, an incidence of 2.8 per cent. Of these 153 women one died, the cause of death being a postpartum hemorrhage.

There were 11 stillborn or deadborn babies, due to the following causes:

Premature separation	5
Intrapartum infection	3
Ruptured uterus	2
Asphyxia	1
Total	11

From Table I it will be seen that the classical section is first, with the low cervical second in frequency. Rarely do we perform vaginal section and almost equally rarely the Latzko.

TABLE I

TYPE OF SECTION	PREMATURE	FULL TERM	TOTAL	% TOTAL
Classical	4	71	75	49.020
Low cervical	1	39	40	26.144
Radical		4	4	2.614
Classical or cervical + sterilization	4	25	29	18.954
Vaginal	1		1	0.654
Latzko		4	4	2.614
Total	10	143	153	100.000

In Table II are given the indications for 153 sections. Indications for cesarean section must be justifiable and the operation must be done at the proper time. If these two requisites are adhered to, what a difference there will be in this country in the incidence of cesarean section and in the maternal mortality rate incident to this operation. The operation of cesarean section is abused not only in respect to incidence, which means faulty and unjustifiable indications, but also in respect to the time of operation. An elective cesarean section should carry with it no maternal mortality. A section done late in labor, done long after rupture of the membranes and done after attempts at other

TABLE II. INDICATIONS

	TOTAL	% TOTAL
Contracted pelvis	80	52.28
Previous section (defective scar)	13	8.50
Premature separation	7	4.58
Placenta previa centralis	2	1.31
Chronic nephritis	13	8.50
Chronic valvular heart disease	10	6.55
Ruptured uterus	2	1.31
Fulminating preeclampsia	3	1.97
Cervical dystocia	6	3.92
Tuberculosis (renal)	1	0.65
Trial of labor (no progress)	3	1.97
Tetanic uterus	1	0.65
Previous myomectomy	1	0.65
Ovarian cyst causing dystocia	1	0.65
Prolonged labor with potential infection	2	1.31
Transverse presentation	1	0.65
Disproportion between fetal head and pelvic inlet	1	0.65
Previous stillbirth	1	0.65
Hydrocephalus of infant	1	0.65
Old pelvic fracture with rupture of bladder	1	0.65
Large infant (breech)	1	0.65
Toxic myocarditis and preeclampsia	1	0.65
Face presentation, chin posterior	1	0.65
Total	153	100.00

types of delivery, carries with it an appalling maternal mortality. Should it become necessary to perform a section after hours of labor, it is imperative that some other type such as a low cervical, or extra-peritoneal operation be done.

In the exhaustive study of maternal mortality in New York City carried out by the New York Academy of Medicine Committee on Public Health Relations, it was clearly brought out what an important rôle the abuse of cesarean section plays in the production of a maternal mortality rate of about 6 per 1,000 live births for that city. Every obstetrician should study that Committee's published report. In it we read: "The incidence of cesarean section in the hospitals of the city is seen to be high—2.2 per cent of all deliveries, while it preceded almost a fifth of all deaths (19.8 per cent). This extremely high incidence in the series is a matter of concern. The indications as given on the records include some, such as toxemia, which some authorities no longer regard as valid. Slight degrees of pelvic contraction, in many instances, do not preclude delivery by the normal route, while malpresentation should rarely make a cesarean section necessary. Dystocia, prolonged labor, and similar terms are not definite ones, and doubt must be expressed as to the propriety of many of the operations undertaken for these reasons.

"More serious and closely related to the indications is the question of the choice of operation and the time of its performance. There is little doubt that in these two elements the greatest danger lies.

"The indications for the cesarean operation need re-statement and further limitation to really valid causes, such as severe degrees of contraction of the pelvis. More careful observation during the prenatal period should provide the opportunity for making a proper prognosis of labor and delivery, and so eliminate the use of the cesarean section as a last resort. The use of the classical type should be limited to the elective operation. The provision of the most highly trained specialist for every woman whose labor shows any abnormality will prevent the use of the cesarean section



when less dangerous methods of delivery could be used by those having the requisite training and skill. Sharp reduction in the number of cesarean sections performed is to be strongly recommended. Where the operation is required, only those whose training in abdominal surgery is adequate to insure proper performance of the operation should be considered suitable operators. Only by this definite narrowing of its use to the legitimate occasion demanding it, as well as the provision of capable operators, can a decrease in these deaths be achieved."

We do the classical operation in cases of elective cesarean section, that is, before the onset of labor and rupture of the membranes. I can see no reason for performing the low cervical operation in elective cases. The lower uterine segment is not very well defined and thinned out prior to the onset of labor; the low cervical operation being, therefore, more difficult and many of these actually result in a modified low classical section. The results in classical cesarean section performed at an elective time before labor gives excellent results.

In order that all of our sections be justifiable on indication grounds, and that most, if not all, be performed at an elective time, because it is in the group of elective sections that our results are the best, it is essential that we study our patients carefully during the last months of gestation in order that we may recognize, before the patient goes into labor, the necessity of operative interference. It is only in the group of elective sections, that we are sure of no ascending infection in the uterus at the time of operation.

Finally, I wish to stress that it takes more knowledge to know and more courage to heed the contraindications to cesarean section. Infection, demonstrable as well as potential, must ever remain before us a danger signal in any contemplated cesarean operation. Those who do not heed it, assume the responsibility of a life. Even with the perfected technic of the extraperitoneal and cervical operations, it becomes a serious undertaking to operate in the face of infection. Cases of this kind are brought to our attention constantly and we cannot make this warning too strong.

Cesarean section has a place in our obstetric armamentarium. Many lives have been, and will continue to be saved, by this operation. Unfortunately, due to the fault of our own profession, this operation, in its abuse, has caused the death of many women. It is clearly our responsibility, as physicians, general practitioners, as well as specialists, to correct this wrong. Let us place this life-saving operation in its proper setting, both in regard to indications, and in respect to time and skill of operation, in order that its abuse may become a legendary affair and our maternal mortality rate within the narrow limits of minimum.

## PRELIMINARY REPORT ON STERILIZATION OF WOMEN BY INTRAUTERINE COAGULATION OF TUBAL ORIFICES\*

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THE sterilization of subnormal women to protect racial integrity is regarded much more important by eugenicists than sterilization of the male. However, the necessity for an abdominal operation or the expense involved, especially in cases where no other operative procedure is indicated or the patient is a poor surgical risk, has been a serious handicap. If, therefore, it were possible to sterilize women in a simple office procedure, it would be of great therapeutic and eugenic value.

The first office procedure in sterilization of women was performed by Dr. Robert L. Dickinson.† By using a semiflexible electric cautery electrode, he was able to produce a burn at the site of the tubal opening of the cornua. The resulting scar tissue frequently blocked the tubal opening. After a period of sixty days the patency of tubes was tested by the Rubin method. Other operators have used chemicals for this purpose. But so far none of the methods have gained the wide use that the importance of the procedure would seem to warrant.

It was, therefore, believed that a coagulating current might be used in the same manner as the cautery and that it would be a safe procedure. A small group of the staff of the Mothers Health Clinic, Miami, Drs. Louise DeVore, Homer Pearson, M. C. Wilson, Buist Litterer, and Lydia Allen DeVilbiss began a series of cases.

The Florida laws contain no reference to contraception or sterilization. However under the Florida law a married woman cannot give legal consent. A release from responsibility similar to that used in hospitals was prepared by a legal firm to be signed by both husband and wife and witnessed. Coagulation of the tubal orifices is always referred to as "treatment." The patients are told that the treatment would probably make the woman less likely to become pregnant and it might prevent pregnancy altogether. After the first year when a number of cases had proved apparently successful, applications for the "treatment," were numerous, many of whom had to be refused because of their youth and lack of therapeutic or eugenic reason.

Coagulation of the tubal orifices requires no anesthesia, being practically painless. Occasionally the patient would speak of a cramping

\*Presented at the Annual Meeting of the Eugenics Association, New York, June 4, 1934.

†J. A. M. A. 92: 373, 1929.

pain but there was no complaint. The patient is accepted for treatment after the menstrual period and is cautioned to come before she has had sexual relations.

#### METHOD

The patient is placed on the table and properly insulated. Under surgical technic a semiflexible uterine electrode is placed in the cornua and a current of varying amperage (approximately 3,500 milliamperes) is applied for fifteen seconds. In the first few patients the current was applied for not more than ten seconds. In these patients the tubes remained patent. The whole procedure, from the time the patient is placed on the table, does not require more than five minutes.

The patient is given a temporary contraceptive to use for the ensuing sixty days when she is requested to come for a Rubin test without having had relations following her menstrual period. This test consists of pumping air into the uterus under measured pressure. In the absence of a Rubin outfit, a surgical house supplied the attachments for an ordinary blood pressure apparatus. If the uterus holds an air pressure of from 150 to 200 mm. for from three to five seconds, the tubes are reported as blocked and the patient considered sterile. When the instrument indicates that air has passed into the tubes or the patient complains of pain under the shoulders within twenty-four hours, she has been given a second treatment and in a few instances even a third without any appreciable ill-effects.

#### RESULTS

The series of 30 coagulation cases was begun in January, 1933. Two of the 8 women of normal intelligence were premenopausal sterilizations.

At the first summary, January, 1934, 20 patients were reported with tubes blocked, 6 tubes patent, 3 no Rubin test, and 1 not treated.

Rechecking all cases as of January, 1935, 17 cases were reported blocked, 9 patent, 3 no test, and 1 no treatment. Seven patients had become pregnant, 3 of whom had been reported blocked, 1 partial blocked, and 3 no test. Two women have moved from the city. Twenty-two are reported nonpregnant, some of whom are using contraceptives.

#### CASE HISTORIES OF 7 FAILURES, (JANUARY, 1935)

CASE 14.—White paralytic moron, husband when drunk kicked her about. Reported blocked. She returned to the clinic pregnant, with signs of an impending abortion at about the sixth week and was sent to the City Hospital. The staff surgeons recommended a hysterectomy. The report of the pathologist follows:

*Gross Pathology.*—Amputated uterus 100 mm. by 70 mm. pale reddish yellow. Cut surface showed a pregnancy in left cornua. The endometrium throughout showed marked thickening with the exception of the area in the right cornua. In this area the surface was flattened and perfectly smooth. Wall of uterus 22 mm. in width.

*Microscopic Pathology.*—Section taken through area in right cornua showed almost complete absence of the epithelial covering with the exception of one place. There were no uterine glands present and the remaining muscle tissue was normal in appearance.

CASE 7.—Colored syphilitic moron, aged twenty-four. Married nine years, 5 pregnancies, 4 living children and 1 dead. Hemorrhage and temperature followed treatment. No Rubin test. No contraceptive or precautions used. Reported four months pregnant.

CASE 20.—White woman, aged thirty-eight, normal intelligence; married eighteen years, 8 pregnancies. Six living children and 2 abortions. Following the coagulation treatment the patient used no precautions against pregnancy and having reported her menses as normal was given a Rubin test sixty days after the treatment. Following the Rubin test she aborted. Subsequently fitted with a diaphragm pessary.

CASE 6.—White syphilitic moron, aged twenty-nine. Married ten years, 3 living children and 2 abortions. Hemorrhage and temperature followed treatment. Rubin test not advised. Given contraceptive which she did not use. Became pregnant and aborted. Fitted with diaphragm pessary which patient is not using but no subsequent pregnancies.

CASE 13.—White moron, aged twenty-seven. Six living children. Following the first treatment the patient's tubes were reported patent. The second treatment was reported blocked. The patient became pregnant and resorted to a criminal abortion. She then began using sheaths. Becoming pregnant again, she had a second criminal abortion performed. In this patient the floor of the perineum is so badly torn that a fitted pessary is not practicable so the patient is using sheaths with lactic acid jelly.

CASE 19.—White, normal intelligence, aged thirty-three. Eight pregnancies, 4 living children, 1 dead, and 3 abortions. Following the first treatment the tubes were reported patent. Following the second treatment the tubes were reported blocked. Using no precautions the patient became pregnant. Referred to a surgeon who, because of her serious physical condition, performed a therapeutic abortion, and a vasectomy on the husband.

CASE 22.—White, cardiac, aged twenty, normal intelligence. Three living children. Following the first treatment the tubes of the patient were reported partially blocked. Patient was given a diaphragm pessary and lactic acid jelly. The patient reported that on one occasion on removal of the pessary she found a good-sized hole in it. She claims this resulted in pregnancy. A previous physician reported that nothing he could recommend would keep this patient from becoming pregnant. Following this delivery surgical sterilization is recommended.

#### CONCLUSIONS

Intrauterine coagulation of tubal orifices is contraindicated in untreated syphilis because of the liability to hemorrhage. It must also be used cautiously in cases of gonorrhea since the blocking of tubes may interfere with tubal drainage, although this infection in itself likely will render the woman sterile. The resulting irritation from the coagulation current may also light up an old infection temporarily. Two such cases occurred in this series. The patients suffered pain and temperature for several days, however without any serious after-effects.

There is no positive assurance that the blocking of tubes with the coagulation method will be permanent. The longest a patient of this series has been under observation is two years.

The intrauterine cautery or coagulation method of sterilization may be recommended where surgery is inadvisable or contraindicated.

## ABDOMINAL CIRCULATION DURING LATE PREGNANCY AS SHOWN IN AORTOGRAMS\*

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SEVERAL years ago the Portuguese physicians, Egaz Moñiz and Dos Santos, astounded the medical world with their work on intra-arterial injections of roentgen opaque substances as a means of establishing the diagnosis of brain tumors and obscure intraabdominal conditions. This method at first was and still is considered audacious, and only few clinics have dared to confirm its value.

In the Urologic Clinic of our hospital we promptly adopted it and since 1930 have employed it frequently (Bisquertt,<sup>1</sup> Coutts,<sup>2</sup> Cantin,<sup>3</sup> etc.) as a means of diagnosis in obscure renal and intraabdominal syndromes.

Conversant with the technic of aortic puncture, we decided to study through injection of the arterial system, the conditions of abdominal organs during the later stages of pregnancy. Twelve normal pregnant women, all over eight months, were submitted to this examination, which from our previous experience we knew to be harmless. Unfortunately one of these women died from meningeal hemorrhage following lumbar puncture.

The technic employed in all cases was as follows: Careful preliminary examination of the patient, especially as regards blood pressure since the intraaortic injection must be performed under spinal anesthesia. Patients with advanced arterial sclerosis are in our opinion unfit subjects for this method, although Bisquertt has obtained successful aortograms in cases of abdominal aortic atheroma and aneurysms. Renal and cardiac diseases, if not very advanced, are no contraindications.

The day before the injection we administer a mild purge and in the morning shortly before taking the aortogram, an enema.

When spinal anesthesia is complete, the patient is turned on the abdomen and her back painted once again with iodine. Four fingerbreadths to left of the spinous processes and anywhere between the first and third lumbar vertebrae, a medium caliber needle from 14 to 15 cm. long is pushed through the mass of spinal muscles until it comes in contact with a vertebral body. The higher up the puncture is made the greater are the chances to inject the celiac axis. The needle is then passed along the surface of the vertebral body. In pregnant women, once the needle has lost contact with the vertebra, it must be slightly tilted to the left, as the aorta has become partially displaced. At this moment the pointed stillette of the needle

\*This paper, contrary to our custom of not accepting contributions from foreign sources, is presented because of the unusual character of the daring experiments made by the authors and their findings.

is withdrawn and the needle pushed forward with increased force in order to penetrate the arterial wall. In some cases, when the displacement of the aorta is not very considerable, it can be penetrated either by continuing the introduction in the original axis or giving the needle a slight inclination to the right.

If we have been successful in the search for the aorta, at the moment of puncture, a red, pulsating stream of blood flows through the needle. Blood flow must now be carefully watched for a few moments in order to ascertain its continuity; without this precaution we may fail to appreciate that the puncture has been incomplete, and when the opaque solution under these conditions is injected it will not enter the aortic lumen, but collect around this blood vessel.

As roentgen opaque fluid we utilize a 75 to 100 per cent solution of sodium iodide. This solution must be injected under pressure of one atmosphere. In order to obtain satisfactory aortograms we found that from 15 to 25 c.c. of the solution are

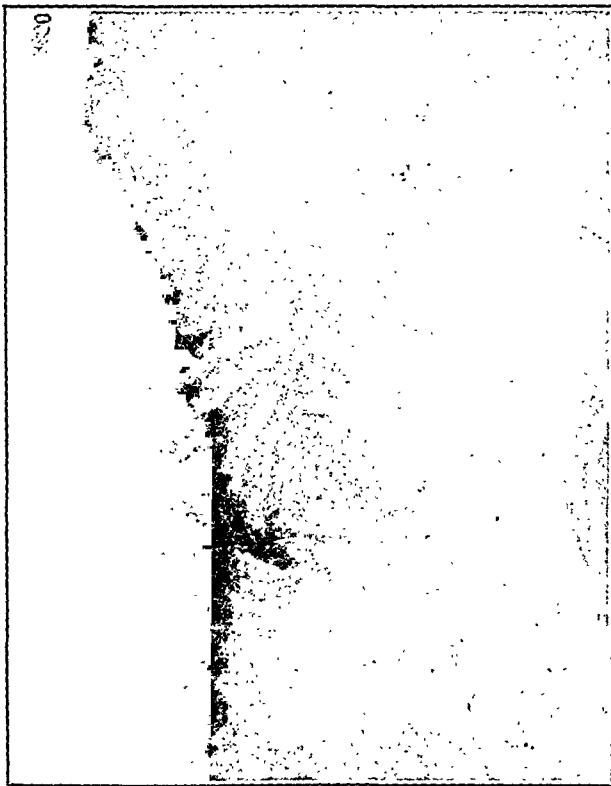


Fig. 1.

required, but if moderately tight rubber bandages are applied around the upper part of both thighs, thus retarding diffusion through the blood stream, 20 c.c. will prove quite sufficient.

Roentgenograms must be taken immediately after injection into the aorta is completed, and the time of exposure must be almost instantaneous. As soon as the radiogram is taken the rubber bandages should be removed.

The immediate effects of the injection are pains in the lower extremities and principally in the feet. Pulse becomes accelerated and soft, but is easily and quickly restored with the use of ordinary stimulants. If the sodium iodide solution should be distributed around the aorta, the patient will experience slight backache for a few days after the accident.

We performed our aortic injections in pregnant women selected from the Clinical Maternity by Dr. Sanhueza Donoso. All fetuses

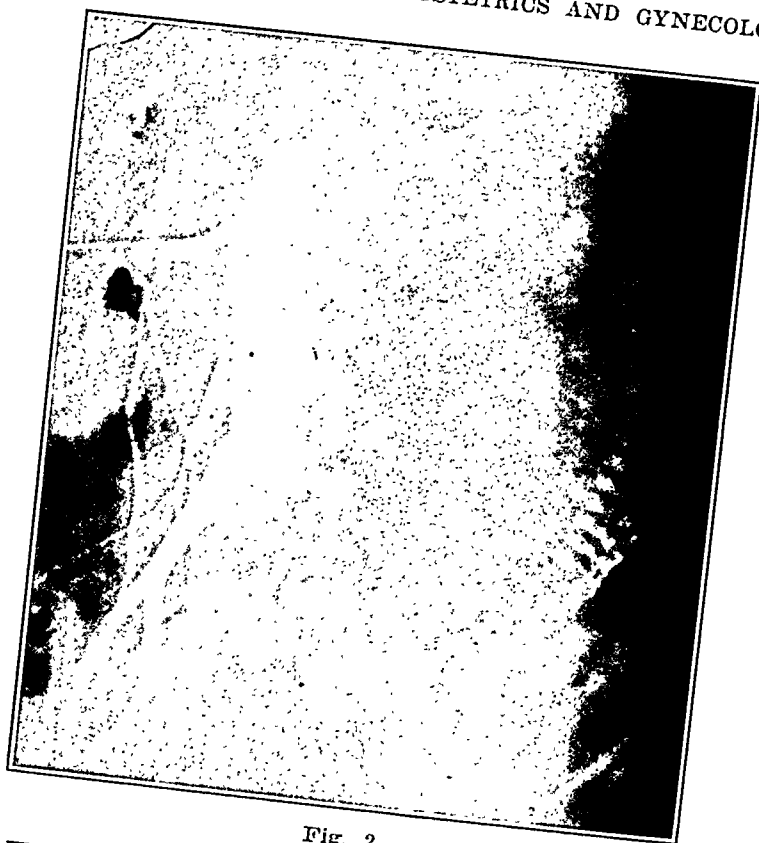


Fig. 2.



Fig. 3.

were carefully controlled before and after the injection through frequent recording of heartbeats; no changes could be detected resulting from the procedure.



Fig. 4.



Fig. 5.

Study of the aortograms taken by us always shows varying degrees of aortic displacements to the left. In Figs. 1, 2, 3, and 4 the renal arteries run in an upward direction, proving that the kidneys are



pushed up by the pregnant uterus. This probably leads to a stretching of the ureters, which under such conditions could be more easily compressed by the distended uterus. Against this supposition, it might be argued that the renal displacement is due solely to the position in which the patient lies while the aortogram is made; this, however, is as well the position more or less maintained during sleep. We then would have to admit that during certain hours of the day this upward pressure on the kidneys possibly does not exist or acts less intensely than during the night.

In Figs. 1, 2, 3, and 5\* definite filling defects in one or other of the common iliac arteries can be noticed. This defect stands in no rela-

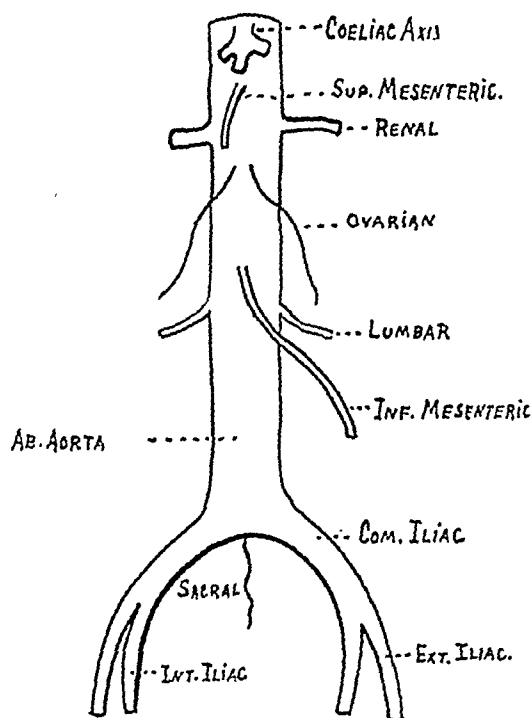


FIG. 6.

tion to the position of the head as can be ascertained by comparing the various illustrations. At first we attributed this phenomenon to pressure against the artery exerted by the pregnant uterus on account of the ventral position in which the patient was placed during the aortogram. Lately we proved through sphygmometric measurings that women in advanced pregnancy show marked differences in blood pressure in the two lower extremities.

The question arises whether this apparent deficiency in the arterial circulation of one side, as demonstrated by aortogram and sphygmometric records, does not result from the drainage of larger quantities of blood on this side through the uterine artery into the placental circulation.

\*The horizontal lines in all the cuts indicate the needle penetrating the aortic wall.

Another fact we wish to point out is the apparent deficient arterial circulation observed in the areas supplied by the colic and sigmoid arteries on the left side. Deficient blood supply for these regions may lead to localized dehydration of intestinal contents and thus account for common constipation in pregnant women. It may also contribute to lower the natural defenses against bacterial absorption, especially of colon bacilli.

In Figs. 1 and 3 we can observe the injection of some placental sinuses; and in Fig. 3 certain vascular structures appear which apparently do not correspond to the maternal circulation and which we, therefore, believe to belong to the fetal circulation. Personally we feel certain that some of them belong to the allantoic arteries.

This modest contribution containing our findings and personal interpretation of ascertained arterial distribution of the abdominal aorta during late pregnancy and symptoms in relation with the changes noted, we present in the hope that it may serve as a basis for investigations and observations of others.

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## DISPROPORTION AT THE PELVIC OUTLET INCIDENT TO FORCEPS DELIVERY

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GR<sup>EAT</sup> resistance to forceps traction is frequently met at the pelvic outlet. Insurmountable obstruction is not always avoidable even with a rigid exclusion of all cases of disproportion. Difficulties are still encountered after the correction of malpositions, and after an accurate biparietal adjustment of the blades, with the application of traction along the proper axis of the birth passage. Repeated failures after careful attention is given to all the technical details, and after all the classical conditions for forceps have apparently been fulfilled, lead one to suspect that not all the factors responsible for failure have hitherto been taken into consideration.

#### FETAL MORTALITY INCIDENT TO FORCEPS DELIVERY IN FUNNEL PELVES

Abundant statistical evidence is available to show that there is a high fetal mortality associated with forceps delivery in funnel pelves.

A study by Burgess,<sup>1</sup> of the results of delivery in contracted pelves, is particularly enlightening. This author presents an analysis of 106 operative deliveries in a series

of 389 cases of funnel pelves. There were 20 fetal deaths in the operative cases, an incidence of 19 per cent. Seventy-three of the operative cases were forceps deliveries. The fetal mortality incident to the forceps deliveries is not given separately, but is undoubtedly considerably higher than the average of 19 per cent for the series.

Similar results are reported by Duncan.<sup>2</sup> This author presents a series of 11 midforceps deliveries among 113 cases of funnel pelves. The fetal mortality in this group of forceps deliveries was 18.1 per cent.

In the San Joaquin General Hospital there were 87 cases of funnel pelves among the last 2,500 deliveries. The classification of funnel pelves was made according to Williams.<sup>3</sup> In this group of funnel pelves there were 11 midforceps deliveries, 5 of which resulted in stillbirths. There was one pubiotomy, one version, and one craniotomy after failure with forceps. There were also 3 cervical cesarean sections after a test of labor and 6 elective sections.

There was no serious preexistent disproportion in the 14 cases in which midforceps delivery was attempted. This is attested by the fact that delivery occurred spontaneously in the remaining 64 cases with similar pelvic measurements.

For purposes of comparison, the midforceps deliveries in normal pelves were also reviewed. There were 34 such cases, and among these there were 5 fetal deaths, a mortality only one-third high as that obtained in the group of funnel pelves.

From the foregoing data, it seems that the obstruction encountered and the resulting failures are due not to preexistent disproportion, but to disproportion inherent in, and peculiar to forceps delivery in funnel pelves.

#### DEFLEXION INCIDENT TO FORCEPS DELIVERY AS A CAUSE OF DISPROPORTION

In funnel pelves, the head usually undergoes slight deflexion when it reaches the midplane. As it approaches the outlet, flexion is gradually reestablished, and finally becomes acute. In consequence of hyperflexion, a segment of the occiput, much narrower than the biparietal diameter, passes between the tuberosities.

In forceps delivery this process of adaptation fails to occur, and flexion remains imperfect. This radical departure from the normal mechanism is due to the circumstance that forceps traction must necessarily be applied along the mentooccipital diameter (instead of the cervicovaginal diameter, along which the powers of labor are normally directed). The "two-armed lever" effect is therefore inevitably lost, and the force of traction is distributed equally to the two poles of the head. The result is that the sinciput is brought to the pelvic outlet simultaneously with the occiput. In consequence of this abnormality the sinciput stems against the tip of the sacrum, and the occiput impinges against the ischiopubic rami before it can reach the tuberosities.

The occiput is thus brought into relation with a transverse diameter of the outlet which is much narrower than the bituberal diameter.

#### THE AVAILABLE TRANSVERSE DIAMETER OF THE OUTLET

Granting that the available transverse diameter is reduced, as a result of deflexion, it is conceivable that there may be an associated compensatory increase in the length of the posterior sagittal diameter.

Measurements were therefore taken in a series of 56 funnel pelves to determine the possible changes in the length of the posterior sagittal diameter, resulting from a displacement of the transverse diameter anteriorly toward the pubis. These determinations were made as follows:

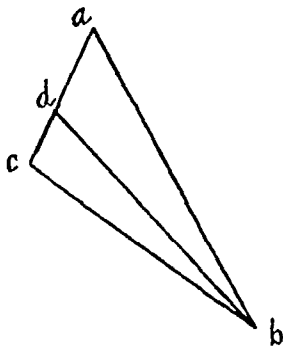


Fig. 1.

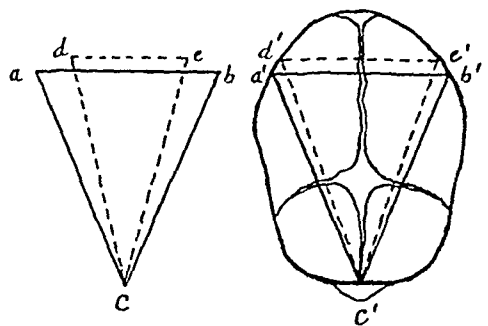


Fig. 2.

Fig. 1.—Sagittal view of pelvic outlet.  $ab$ ,  $bc$ , and  $ac$ , represent the sacropubic, the posterior sagittal, and the anterior sagittal diameters, respectively.  $bd$  represents the posterior sagittal diameter when the transverse diameter is advanced toward the pubis. The gain in length of the posterior sagittal ( $bd$ ), at any particular level depends chiefly on the relative length of the sacropubic and posterior sagittal diameters,  $ab$  and  $bc$ , respectively.

Fig. 2.—Cephalopelvic relation at the outlet.  $abc$  is the triangle of the outlet, formed by the tubera of the ischium ( $ab$ ), and the tip of the sacrum ( $c$ ).  $a'b'c'$  represents the corresponding triangle of the head. The two triangles are equal; there is no disproportion.  $dec$  is the triangle of the outlet when the transverse diameter is advanced so far toward the pubis that a reduction of 3 cm. in its width results.  $d'e'c'$  represents the corresponding triangle of the head. The triangle of the head is much larger than the triangle of the outlet; there is marked disproportion.  $\times \frac{1}{4}$ .

The bituberal and posterior sagittal diameters were measured in the usual manner by means of a pelvimeter and a series of gauges previously described.<sup>4</sup> In each instance a gauge, 3 cm. narrower than the bituberal diameter in the particular case, was fitted between the pubic rami, and the posterior sagittal diameter was again measured. It was found that there is an increase of only 0.2 to 1.0 cm. (average 0.48) in the length of the posterior sagittal diameter at the new level; the increase being practically negligible in pelves with a narrow sacropubic diameter (Fig. 1). It is obvious, then, that if the transverse diameter of the outlet is advanced anteriorly toward the pubis, much more is lost in its width than is gained in the length of the corresponding posterior sagittal diameter. The result is that the head is forced to pass through a triangle of the outlet which is much smaller in area than that formed by the tubera of the ischium and tip of the sacrum (Fig. 2).

## TRANSVERSE DIAMETER OF THE PRESENTING PART

In consequence of the slight increase in the length of the posterior sagittal diameter coincident with the anterior advancement of the transverse diameter, a segment of the occiput which is considerably reduced in width is brought into relation with the pelvic outlet. It is, therefore, necessary to determine to what extent this diminution in the transverse diameter of the presenting part can compensate for the narrowing of the available transverse diameter of the outlet. This was determined as follows:

The parietal bosses were marked, and the biparietal diameter was measured between these points in the usual manner. Points were then marked on the occiput 2 cm. from the original markings, in a straight line toward the occipital protuberance, and the distance between these points was likewise measured. These measurements were taken in 55 newborns six to nine days old. It was found that on an average the width of the occiput as measured in the manner described, is only 0.72 cm. less than the width of the biparietal diameter. It is clear, therefore, that the gain in length of the posterior sagittal diameter, plus the coincident reduction in the width of the presenting part, compensates for less than one-half of the disproportion resulting from the loss in the width of the available transverse diameter of the outlet (Fig. 2).

## THE NARROW SACROPUBIC DIAMETER

The disproportion resulting from deflexion is even greater in funnel pelves with a coexistent contraction in the sacropubic diameter. This is due to the circumstance that the compensatory gain in length of the posterior sagittal diameter is less when the sacropubic diameter is relatively narrow (Fig. 2). In consequence of the shortness of the posterior sagittal diameter the presenting part is advanced anteriorly toward the pubis, and a wider segment of the occiput is brought into relation with the transverse diameter of the outlet. The loss in length of the posterior sagittal diameter, coupled with the increase in width of the presenting part, thus, adds greatly to the disproportion in funnel pelves (Fig. 2).

## PRACTICAL BEARING ON TREATMENT

The foregoing analysis of the mechanism of labor shows clearly that pelves with outlet measurements adequate for spontaneous delivery, may be much too contracted for forceps delivery. The minimum values for the dimensions of the outlet used at present as a basis for the management of labor in funnel pelves<sup>3</sup> should, therefore, be considerably raised when applied to forceps delivery, particularly in pelves with a narrow sacropubic diameter. The high fetal mortality reported in the recent literature demands a wider margin of safety for forceps delivery than that taken heretofore.

Even under the most favorable circumstances, the forceps should, however, be regarded as a poor substitute for the normal powers of labor. If delivery through the natural passages is decided upon, a policy of ultraconservatism should therefore be followed, and the forceps should be held in reserve to be used only on the strictest indications. Forceps delivery in funnel pelves should be regarded as a hazardous undertaking, and as a procedure of necessity; not as one of choice or "convenience."

## SUMMARY

1. Attention is called to the fact that there is a high fetal mortality incident to forceps delivery in funnel pelves.

2. A study of the mechanism of labor in funnel pelves is presented which indicates that the obstruction encountered in forceps delivery is usually due not to preexistent disproportion, but to disproportion resulting from deflexion incident to forceps traction.

3. Deflexion is particularly likely to result in disproportion when there is a coexistent contraction in the sacropubic diameter.

4. The present study substantiates the view long entertained that forceps delivery is usually contraindicated in funnel pelves.

## ADDENDUM

*The occipitoposterior position.*—In reviewing the case histories since the manuscript was submitted for publication I observed that in 9 out of the 14 cases of attempted forceps delivery in funnel pelves, labor was complicated by the occipitoposterior position. The malposition was corrected in every one of these cases preliminary to forceps traction; some degree of deflexion characteristic of occipitoposterior positions, however persisted. The disproportion in these 9 cases must, therefore, be attributed in part to the faulty attitude originally associated with the posterior position, which forceps traction failed to correct.

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Morrison, Marriott T.: Chancre of the Cervix, Am. J. Syph. & Neurol. 18: 196, 1934.

Primary chancre of the cervix, if looked for, is likely to show an incidence of 14 per cent to 18 per cent of all infectious syphilitic lesions in the female. Three-fourths of the cases of primary cervical chancre have gross physical findings that are characteristic. The dark-field examination is the most useful diagnostic procedure.

C. O. MALAND.

## SECONDARY PURPURA HEMORRHAGICA COMPLICATING PREGNANCY

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**P**URPURA hemorrhagica is, according to the literature, a rare but not infrequent complication of pregnancy and the puerperium. The purpuras have been classified by Pratt (*Modern Medicine*, Osler and McCrae, ed. 2, p. 687) into two main groups: the primary and the secondary. The primary, or, as it is better known, idiopathic thrombopenic purpura, is due to a disturbance of the physiologic function of the spleen. In the secondary type, the purpura is a symptom of a known disease or condition, or related to it.

The following two cases were observed in the University Hospital and are presented in the hope that they may answer some of the questions of similar cases.

CASE 1.—Colored female, aged nineteen, admitted Nov. 25, 1931, complaining of lower abdominal cramps. She was one of fifteen children, ten of whom were living and well, the other five having died as children from upper respiratory infections. Her father died at sixty-two from diabetes and her mother at fifty-four from cardiac disease. She had had measles and mumps during childhood. She contracted both syphilis and gonorrhea shortly after her marriage, in 1928, at fifteen years of age. She was delivered at term of her first child, Feb. 17, 1931, after a normal labor. The child was normal. During her pregnancy and up to the time of her present admission she had been under treatment for her two venereal diseases. The patient menstruated May 16, 1931, three months after her delivery, and became pregnant shortly thereafter, the expected date being Feb. 23, 1932. The pregnancy progressed uneventfully. She visited the dispensary on November 5 and at that time was well. On November 25, about 10 A.M. she began to experience lower abdominal cramps simulating labor pains and was admitted to the hospital at 12:30 P.M. On admission the temperature was 98.2° F., pulse 64, and respiration 20. The general physical examination was negative. The uterus was the size of a seven months' pregnancy. No fetal heart could be heard. Believing the patient to be in threatened labor she was given morphine sulphate grains  $\frac{1}{4}$  and scopolamine grains  $\frac{1}{150}$ . At 4 P.M. there occurred a sudden vaginal hemorrhage of about 500 c.c. The uterus was firmer than previously, of the size of an eight months' gestation, and contracting at irregular intervals. The cervix was thin, dilated one finger, but there was no evidence of placenta previa. Shortly after this the patient began to bleed from the mucous membranes of the nose, mouth, and rectum. The urine was clear, acid, specific gravity, 1.016, albumin and sugar negative and microscopically negative. The hemoglobin was 61 per cent (Sahli); R.B.C. 3,500,000; the bleeding time (Duke) was three hours; and an intravenous specimen of blood taken for typing had not formed a clot fourteen hours later. Blood platelet count unfortunately was not done.

At 6 P.M. the pulse was 64, the blood pressure 70/50, and the patient was pale and restless. There was frank hemorrhage from the gums and the patient vomited large quantities of coffee brown material several times. The uterine contractions were every ten minutes and the uterus was stony hard with fundus almost to the ensiform. There was only slight vaginal bleeding. The cervix then was thin and dilated 3 cm. with membranes protruding through the os.

A diagnosis of premature separation of the placenta with retroplacental hemorrhage, complicating or complicated by a purpura, was made. To lessen uterine tension, the membranes were ruptured artificially and a tight binder applied. Labor progressed rapidly and at 8:50 P.M. the patient delivered herself of a stillborn premature female. Following the delivery of the fetus the placenta and many large blood clots were expelled. The placenta showed definite signs of a premature separation.

The uterus contracted well but in spite of pituitrin, ergot, and thromboplastin the bleeding continued. The uterine arteries were ligated by the vaginal route. The uterus and vagina were packed tightly. While this was being done the patient received 1,000 c.c. of normal saline intravenously, followed immediately by 500 c.c. of citrated blood. Continuous hypodermoclysis (2,000 c.c.) was carried out through the night and the patient was given two 15 c.c. doses of thromboplastin. All hemorrhage was well controlled by the next morning, when she was given another transfusion of 450 c.c. of citrated blood. Calcium lactate was given four times daily in 10 gr. doses. The bleeding time was now three minutes and venous blood coagulated in six minutes with a normally firmly retracted clot. The platelet count after the second transfusion was only 158,000.

On November 27 the hemoglobin was 35 per cent and the R.B.C. 2,500,000. There was no further bleeding. A third transfusion of 450 c.c. of citrated blood was given. The vaginouterine pack was removed on November 28. The patient made an uneventful recovery and was dismissed from the hospital December 9, the fourteenth day. The hemoglobin was 53 per cent and the R.B.C. 3,000,000.

The patient was advised to continue her antisyphilitic treatments, calcium by mouth, diet and not to become pregnant. She faithfully performed the first two injunctions but became pregnant during June, 1932, as her last period occurred June 1. The expected date of delivery being estimated as March 8, 1933. During the pregnancy she received the quartz-light weekly, cod liver oil with viosterol 1 c.c., and calcium lactate 10 gr. daily. She also continued her antisyphilitic treatments. The pregnancy proceeded normally until Feb. 5, 1933, when she had a small vaginal hemorrhage of about one hour in duration and just enough to saturate several pads. She was admitted to the hospital. Examination revealed an uterus the size of an eight months' gestation. The fetal heart rate was 140. The placenta souffle was heard in the lower left abdomen just above the symphysis. Vaginal examination failed to reveal any further evidence of placenta previa. The urine was negative. Bleeding time was three minutes, coagulation time three and one-half minutes, platelet count 320,000, and blood serum calcium 10 mg. per 100 c.c.

There was no further bleeding and the patient was dismissed February 8. She was readmitted March 13, 1933, for induction of labor. The bleeding time was three minutes; the coagulation time, nine and one-half minutes; the platelet count, 250,000; the hemoglobin, 61 per cent, and the R.B.C., 4,000,000.

On March 15 she was given 10 c.c. of a 10 per cent calcium gluconate solution intravenously. A medical induction was done March 16 but was unsuccessful. The induction was repeated March 18, and the patient fell into active labor. When the cervix was almost fully dilated she was given another 10 c.c. of 10 per cent calcium gluconate intravenously. She delivered herself spontaneously of a normal male child. The placenta was expressed, and there was only about 150 c.c. of hemorrhage, the blood clotting almost immediately. She was dismissed on the tenth day and has continued to be well without further purpuric symptoms and without treatment.

CASE 2.—White, aged thirty-three, admitted May 8, 1933. The patient had had measles, mumps, smallpox, and scarlet fever. She had had five previous pregnancies, all normal and without any complication. The family history was negative. The last menstrual period began Sept. 25, 1932, following which there was complete



amenorrhea. Quickening was noted in February. There had been occasional headache and vertigo. For three days prior to admission there had been headache, vertigo and some nausea, and she experienced some false labor pains. On the morning of admission while doing some housework she fainted. On regaining consciousness she vomited several times, the vomitus containing coffee brown material. She also noticed a diffuse bilateral conjunctival hemorrhage with a large ecchymosis of the soft tissues surrounding each eye. Nausea, vomiting, and vertigo continued. Labor pains recommenced and she was admitted to the hospital.

On admission a physical examination revealed a fairly well-nourished female who appeared quite ill. There were present the diffuse subconjunctival hemorrhages and ecchymoses of the eyes, each area about 6 cm. in diameter. The fundus of each eye was negative except for slight edema. All the teeth of the upper jaw had been removed, but the lower teeth showed considerable caries. The heart and lungs were negative. The blood pressure was 108/80. The abdomen was enlarged by a seven and one-half months' gestation. The uterus was contracting at irregular intervals. No fetal heart tones or placental souffle could be heard. On rectal examination no dilation or effacement of the cervix could be determined. The extremities were negative except for a large ecchymosis on the dorsum of the right foot.

The urine on a catheterized specimen was of reddish color, 1,020, acid, sugar negative, albumin 2-plus; on microscopic examination there was a rare leucocyte, 30 to 70 R.B.C. per high power field, and many granular casts. The blood Hb. was 65 per cent (Sahli); R.B.C., 3,280,000; W.B.C., 8,000 with a normal differential; platelets 142,000. Coagulation time nine minutes, bleeding time 5.5 minutes. Blood serum calcium 8.9 mg. Nonprotein nitrogen 29 mg. per cent. Wassermann negative. The labor pains disappeared a few hours after admission, the nausea and vertigo ceased. On the following day the patient felt much improved, there was no further vomiting, and the urine appeared macroscopically less red. There appeared, however, a large crop of petechiae over the lower right abdominal wall, and around the neck with a few isolated areas elsewhere.

On May 12 (the fourth day) the petechiae were fading but there was no change in the eyes. The urine had cleared entirely of blood. Fetal movements were absent and no heart tones could be heard. On May 15 there was a slight icteric tint to the skin. On May 19 at 5 A.M. the patient fell into actual labor and delivered spontaneously at 10 A.M. of a dead born macerated fetus. The placenta separated spontaneously and was delivered intact. There was very little bleeding, the uterus contracting well. There were no further purpuric manifestations and the eyes cleared gradually. The patient was dismissed on May 29, and has remained well to date.

#### DISCUSSION

CASE 1.—The cause of the purpura here is not definitely proved but thought to be on a toxic basis. The possible origins of the toxin are:

1. Arsenic from the antisyphilitic treatment, but there had been no treatment for ten days.

2. Metabolic, as a result of disturbance of metabolism brought about by pregnancy, similar to the toxins causing the various toxemias of pregnancy.

3. Metabolic, as a result of the retroplacental hemorrhage associated with the ablatio placentae. Possibly some change in the blood proteins was brought about with the accumulation of large amounts of blood behind the placenta and undoubtedly infiltrating the uterus. This was reabsorbed by the body tissues and purpura resulted.

An argument in favor of this particular origin is that the onset was so abrupt with no prodromal symptoms.

This case is particularly interesting in another way, and that is the patient's safe conduct through a subsequent pregnancy with many prophylactic measures instituted to prevent the recurrence of the purpura. The majority of patients die as a result of the first attack of purpura during their pregnancy. Repeated pregnancies, therefore, are a little unusual.

CASE 2.—Here as in the first case the etiology is unknown but again presumed to be toxic and probably metabolic on the same basis as the other toxic conditions of pregnancy.

The onset was slow with prodromal symptoms, the course much milder, and the patient received practically no treatment. This is of course in great contrast to the first case.

IMMANUEL DEACONESS INSTITUTE

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## PREGNANCY AFTER NEPHRECTOMY

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H. B. MATTHEWS<sup>1</sup> has collected 241 cases of nephrectomized women with 265 labors, of which 250 were normal and 15 were complicated. Two of his patients died.

He argues very strongly that there was no indication for the immediate termination of pregnancy on discovery of nephrectomy in the patient. He concludes that pregnancy after nephrectomy follows its normal evolution, and that it is little more hazardous for the mother and child than pregnancy under normal conditions, providing the remaining kidney is functioning properly. In cases where nephrectomy has been performed for renal tuberculosis, it is imperative to ascertain whether the patient is free from symptoms of tuberculosis in the bladder, ureter, remaining kidney, and lungs for three or more years before pregnancy is allowed to supervene. Pregnancy after nephrectomy for carcinoma should not be allowed under any circumstances. Pregnancy after nephrectomy should be terminated immediately on the advent of frank renal insufficiency. An albuminuria varying from slight to very marked is to be expected in a certain proportion of cases in the last four or six weeks of pregnancy. This clears up under appropriate treatment.

Kanter and Klawans<sup>2</sup> in a recent paper on sterilization claim that tuberculosis of the kidney precludes pregnancy even though the focus of infection has been removed by nephrectomy. They hasten to add that they do not mean that every case of nephrectomy calls for sterilization. They have had several cases of women with nephrectomy who were successfully delivered and who made an uneventful recovery. Therefore, they say that previous nephrectomy is not an indication for sterilization unless in cases where the kidney has been removed for tuberculosis or where the function of the remaining kidney is found by laboratory test to be below normal.

Matthews suggests that a more scientific study of the nephrectomized woman be made and that a well "worked-up" report, including all laboratory methods for the determination of kidney function and urinary excretion, should be published of every case of pregnancy after nephrectomy.

Therefore, I am presenting the following case of a pregnant woman with a left nephrectomy for pyonephrosis performed eight years before pregnancy. The case is further complicated by the fact that the woman was extremely obese, aged forty-one years, and a primipara.

E. H. (No. 37523), colored, forty-one years of age, admitted to the Obstetrical Service of Harlem Hospital from the Out-Patient Department on Oct. 27, 1933, at 7 P.M. She complained of dizziness and of having fainted five days previously. The same picture was repeated two days later and upon attending the Out-Patient Department she was asked to come into the hospital.

Patient had had appendectomy performed in 1914. In addition a left nephrectomy for pyonephrosis was performed in Pittsburgh in 1925.

She had an epistaxis twice in August, 1933, and once in September and once (slight) two days before admission. In addition patient claimed palpitation of the heart for a month up to admission. Nausea and faintness and edema of ankles for same period. Her last menstrual period was February 9, 1933, lasting five days. Previous menstruation normal. Para 0, abortions (induced) 4, gravid 5. Pregnant eight months. Examination showed an extremely obese colored woman, weight 218 pounds.

Blood pressure 180/95. Temperature 98.7° F. Pulse 90. Urine: Sp. Gr. 1,018, reaction acid, albumin +++, very many leucocytes. Blood chemistry: creatinin, 1.3 mg. per 100 c.c. blood, urea 8 mg. per 100 c.c. blood, sugar 103 mg. per 100 c.c. blood. Kahn test negative.

Upon a diagnosis of preeclampsias, a Mosenthal test was done and repeated several times. The first Mosenthal test, from urine taken October 29, 12 M. to 8 P.M., showed a specific gravity varying from 1,004 to 1,010.

The pelvis was ample, the presentation vertex, and the fetal position L.O.A.

The patient was kept in bed, bromides and chloral hydrate prescribed, and a low protein content, salt-free diet ordered.

Two hours after admission blood pressure dropped to 160/95. Blood pressure on the day following admission was 136/90, temperature and pulse flat. Urine showed Sp. Gr. 1,012, faint traces of albumin, a few leucocytes. No edema was present.

Three days after admission a urologic consultation was held, and blood pressure remaining normal, urine proving albumin-free, no edema manifesting itself, and a repeated Mosenthal test indicating normal kidney function, it was decided to allow the patient to go to term rather than end the pregnancy.

On the eighth day after admission blood pressure, pulse, temperature, and urine were essentially negative. At this time it was thought that a cesarean section with sterilization might be performed in view of the patient's age (forty-one) and primiparity. The patient was unwilling to give any information about her husband so that his consent might be obtained in writing. It was, therefore, decided to allow the patient to go to term and perhaps deliver spontaneously. A Mosenthal test was taken on the eighth day and revealed a variation in specific gravity of 1,008 to 1,020 in twenty-four hours.

Blood pressure and urine remained normal until the twentieth day after admission. On that day at 12:25 A.M., the membranes ruptured spontaneously. Labor pains did not begin until 1 P.M. The first stage of labor lasted until 7:30 A.M. the next day, or twenty-one hours.

At 10 A.M. the cervix had been fully dilated for more than two hours, and large quantities of meconium were passed. The head was on the perineum, and the patient was having strong pains but making no progress. The blood pressure was 170/110, and the fetal heart was 180. A fibroid 4 cm. in diameter was palpated on the left cornu of the uterus.

In view of these signs of preeclamptic toxemia, fetal distress, age, and primiparity of the patient, a low DeWees forceps delivery was done. A male infant weighing 8 pounds 6¼ ounces was delivered. A tight loop of cord around the neck was freed and resuscitation successfully applied.

There was a first-degree laceration of the perineum. The placenta was expressed thirty minutes after delivery and 1 c.c. of pituitrin and gynergen was administered.

The day following delivery the blood pressure was 144/88, urine findings were negative, and the general condition was good.

Three days after delivery the patient complained of pain in the left chest, but examination was negative. Two days later blood pressure, temperature, pulse, and urine were normal. There was a profuse lochia, slightly foul, the abdomen was slightly distended, and the fundus was two fingers below the umbilicus.

On the sixth day postpartum the patient complained of drowsiness and night sweats but no cough. Blood pressure, pulse, and temperature were normal, and the urine showed a specific gravity of 1,018, albumin ++, and a moderate number of leucocytes.

The next day the patient complained again of profuse night sweats, but the general condition was good. Breasts were moderately engorged and tender. Abdomen was relaxed, the fundus was well involuted and firm. Lochia was profuse and foul. Blood pressure, pulse, and temperature were normal. Urine showed specific gravity 1,018, albumin +, and a few epithelial cells.

On the tenth day, the thirty-first day after admission, the patient left the hospital.

The patient returned to the follow-up clinic four weeks later having worked as housekeeper for the past two weeks. Blood pressure 150/90. Vaginal examination: perineum healed and firm, introitus roomy, cervix smooth and closed, uterus anterior, freely movable, well involuted, small fibroid felt on fundus, adnexa negative. Urine: color straw, clear, Sp. Gr. 1,024, trace of albumin, glucose negative, few epithelial cells.

April 16, 1934: Patient had continued working. Examination negative. Urine: color straw, Sp. Gr. 1,016, albumin +, glucose negative. Microscopic examination of urine: few epithelial cells, occasional white blood cells, acetone negative, diacetic acid negative. Blood chemistry: creatinine 1.3 mg. per 100 c.c. blood, urea nitrogen 9.6 mg. per 100 c.c. blood, sugar 96.0 mg. per 100 c.c. blood. Blood pressure 130/90.

#### CONCLUSIONS

Despite nephrectomy, advanced age, obesity, and primiparity of the patient, she was successfully delivered of a living child with the use of low forceps.

Albuminuria, high blood pressure, vertigo, and edema were cleared up prior to delivery by use of low protein content, salt-free diet, and rest.

The patient was carefully watched by means of constant blood pressure readings, urinalyses, and repeated Mosenthal tests for insufficient kidney function. The determination was to terminate pregnancy immediately if these manifested themselves.

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1132 PARK AVENUE

# SUDDEN DEATH DUE TO PULMONARY EMBOLISM IN A CASE OF PUERPERAL ENDOMETRITIS ASSOCIATED WITH UNSUSPECTED SUPPURATION IN THE RUPTURED SYMPHYSIS PUBIS\*

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**S**EPARATION of the symphysis during labor or delivery is not uncommon, but suppuration into the ruptured symphyseal joint is of rare occurrence, and it is the accidental finding of this condition at autopsy that warrants this case report.

F. B., a white American housewife twenty-four years old, was admitted Feb. 7, 1934, with a history of ruptured membranes for four hours and mild pains for six hours. The patient had been attending the prenatal clinic and the pregnancy had been normal throughout the antepartum course. The family history and past medical history were completely negative except that she had undergone two operations previously; a thyroidectomy two years before and the removal of an ovarian cyst and appendix one year before. The menstrual history was normal, the last normal period May 2, 1933, the expected date of confinement Feb. 9, 1934. She had had two full-term living children. The first of these was a spontaneous delivery after a three-day labor; the second was a low forceps delivery after an eighteen-hour labor. No suturing was required after either delivery and the postpartum course was perfectly normal each time.

Physical examination at time of admission showed a well-developed woman. Temperature, pulse, and respirations were normal. Blood pressure was 110/70. Abdominal examination revealed an old scar in the lower midline and a full-term uterus with the fetus in the L.O.A. position. The fetal heart sounds were in the L.L.Q., 140 and regular. The vertex was floating. The external measurements were: interspinous 21, intercrystal 26, right oblique 21 cm., left oblique 21 cm., and external conjugate 17.5 cm. Vaginal examination revealed a moderate cystocele, the cervix was thick, uneffaced, one finger dilated, and the promontory was easily reached. The outlet seemed to be ample. The diagonal conjugate measured 11.5 cm., giving a true conjugate of about 10 cm. The baby was not big, and as the head could be very easily pressed into the brim, the impression was that delivery would easily occur from below, once real labor set in.

For the next thirty-eight hours the patient continued to have moderately severe uterine contractions at five- or six-minute intervals. These had no effect on the cervix, which remained thick, uneffaced, and one-finger dilated; and the vertex remained high and unengaged. During this period she was given two doses of  $\frac{1}{6}$  gr. of morphine and  $\frac{1}{450}$  gr. of scopolamine, each of which gave her about three hours of rest. After the second injection had worn off, a hot soapsuds enema and 2 ounces of castor oil were given, with the hope of initiating effectual uterine contractions, but without success. Temperature, pulse, and respirations were still normal, blood pressure 110/70, urine negative, and the patient was taking food and fluids well.

Forty-four hours after the onset of pains, the patient was taken to the delivery room and a No. 5 Voorhees bag was easily inserted into the cervix without any anesthesia. The patient was then put back to bed and a one-pound weight was at-

\*Presented at a meeting of the Brooklyn Gynecological Society, May 4, 1934.

tached from the bag over the lower pole of the bed. This was followed by fairly strong contractions in about one and a half hours and the bag was expelled eight hours after its insertion. A full-term normal baby in the L.O.A. position was born spontaneously two hours after the expulsion of the bag. No anesthesia was used. There were no soft tissue tears at the time of delivery. The placenta and membranes were delivered spontaneously and apparently completely, ten minutes after the birth of the baby. The total blood loss was about 200 c.c. Both pituitrin and gynergen were given hypodermically after the expulsion of the placenta as the uterus showed a tendency to relax. This was supplemented with fluid extract of ergot.

The duration of the first stage was fifty-four hours, the second stage a little less than an hour, and the third stage ten minutes. The number of vaginal examinations was 3, rectal examinations 10. At time of delivery the temperature was 101.4°, pulse 100, respirations 20.

Second Day Postpartum: Temperature 102.6°, pulse 120, respirations 24. Patient complaining of pain in lower abdomen over the symphysis and across the lower back. Could not lift legs or turn on side without excruciating pain in the symphysis, back, and along both thighs and legs. Physical examination revealed a definite separation of the symphysis with marked tenderness over the symphysis pubis and over both sacroiliac regions. An x-ray taken on this day showed "slight diastasis of the symphysis pubis and slight downward displacement of the left pubis." The pelvis was tightly strapped with adhesive in the form of a many-tailed binder with marked relief of symptoms. This strapping made it possible for the patient to turn and to move her legs after it had been on for twenty-four hours. After this, the pain and tenderness gradually disappeared, and the strapping was removed eight days after its application. At the time of its removal, the symphysis still felt separated, but all symptoms were gone.

The patient ran three complete cycles of temperature of three days each, the temperature fluctuating from 101° to 103.5°. The lochia remained scant and foul, the uterus subinvolved, and there was moderate tenderness over both parametrial areas and also over the symphysis. The treatment during these ten days consisted of immobilization of the pelvis, high Fowler's position, ergot, fluids, ice bag, codeine and aspirin for pain, and sodium amytal for rest at night. There were no chills at any time.

On the tenth day postpartum, the temperature came down to normal and after fluctuating from 98° to 100° for two days, it remained normal after the twelfth postpartum day. On the fourteenth day the patient was allowed out of bed for a short time. After being up for about fifteen minutes, she walked to the bathroom, which was only some ten feet away, and shortly called the nurse, stating that she felt very faint. The nurse put the patient's head between her knees and in doing so, noticed that the patient was unconscious. She was carried back to her bed by nurses and internes. Patient was in coma, and pulse very rapid, thready, and feeble. She was very pale and cyanosis developed rapidly about the nose and mouth. Adrenalin, intramuscularly and intracardiac, were given. Oxygen and artificial respiration met with no response. Patient was pronounced dead twenty-five minutes after complaint of feeling faint.

The autopsy showed neither the peritoneal nor the pleural cavities with free fluid or adhesions.

The lungs were reddish blue in color; there was marked congestion and edema at the bases; the left lower lobe showed a few small reddish patches of consolidation which appeared to be an early bronchopneumonia. In the lower half of the left lower lobe there was an area about two inches in diameter which was dark red, firm, and sharply demarcated from the rest of the lung. On opening the branch of the pulmonary artery running into the left lower lobe, there was found to be a large

embolus, well organized, grayish red in color, and adherent to the vessel wall. The pericardial sac contained about 20 c.c. of fluid blood, and there was a needle puncture on the anterior surface of the right ventricle. The heart was normal in size; the myocardium was pale red and firm on section. The cardiac valves showed no gross pathology. The aorta was grossly normal. The spleen was enlarged, weighing 220 gm. Its surface was slate blue. On section, the pulp was dark red, soft, and pul-taceous. The liver was of normal size; surface was smooth, but was rather soft in consistency. On section, the parenchyma was of a mahogany red color, with areas of yellowish mottling scattered throughout. The kidneys were normal in size; capsules stripped easily, leaving smooth surfaces. On section, the cut surfaces were light red in color; cortices were normal in size, markings stood out prominently. Gastrointestinal tract showed no gross pathology.

Uterus was enlarged to about the size of a three and a half months' pregnancy, the fundus extended about two inches above the pelvic brim and was soft in consistency. The cervix showed no lacerations or erosions. On opening the uterus, there was found an area 2 x 2 inches on the upper posterior wall which was covered with reddish black, soft, friable tissue which was adherent to the uterine wall. Sections through this area showed a purulent exudate in the walls of the uterus.

The veins of the right broad ligament were enlarged, thickened, and filled with blood clot. The right ovarian vein was thickened to about the size of one's thumb finger and was filled with an organized thrombus. The iliac veins appeared normal. Tubes and ovaries appeared grossly normal. On section, the ovaries were found to be fibrocystic.

There was a marked separation of the symphysis pubis in the midline and upon incising the symphyseal joint, about one dram of thick, yellowish, odorless, purulent exudate escaped. There was no evidence of any infection in the space of Retzius nor was there any gross evidence of any osteomyelitis of either pubic bone.

*Anatomic Diagnosis.*—Congestion and edema of lungs; bronchopneumonia; pulmonary embolism; hemorrhagic infarction of lungs; cloudy swelling of heart, liver, and kidneys; congestion of spleen; septic metritis and endometritis; thrombosis of veins of right broad ligament and right ovarian vein; chronic fibrocystic oophoritis; and separation of symphysis pubis with suppuration.

*Cause of Death.*—Pulmonary embolism following septic endometritis and metritis.

1325 UNION STREET

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Hirsch-Hoffman: The Development of Tuberculosis of the Female Genitalia and Peritoneum in Primary Infections of the Intestinal Tract, Arch. f. Gynäk. 153: 375, 1933.

The author does not believe that primary tuberculosis of the female genitalia exists, but that all genital infections are secondary. Such secondary infection may result from contact, from extension of peritoneal infection to tubal lumen or by way of the lymphatics or the blood stream. The comparative frequency of these four methods of infection is unknown. The author reports the results of his experimental work on rabbits and his studies on some of the nurslings who died during the ill-fated tuberculosis inoculations in Luebeck.

He concludes that in severe primary intestinal tuberculosis the peritoneal infection is primarily lymphogenic. In infection of the female genitalia the infection may be lymphogenic or hematogenous in origin. The transtubal development of tuberculous infections of the female genitalia is much less frequent than are the lymphogenic or hematogenous infections.

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BILATERAL URETEROVAGINAL FISTULA

SUCCESSFUL IMPLANTATION OF BOTH URETERS INTO THE BLADDER  
SEVEN AND ELEVEN MONTHS FOLLOWING TOTAL HYSTERECTOMY

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IN ALMOST all the cases of severance of the ureter, recognized during operation, there is a possibility of repairing the damage by ureteroureteral anastomosis ligature, or implantation of the ureter into the bladder. In a small number of these cases and in cases of partial damage to the wall of the ureter, however, a ureterovaginal fistula may develop, which is the unavoidable outcome if the injury of the ureter has not been recognized during operation. There is a chance that a ureterovaginal fistula may heal spontaneously either with full function of the kidney or by autonephrectomy as much as three months following operation. After this time a secondary implantation has to be attempted. According to Bland, secondary implantation, owing to envelopment of the damaged end of the ureter in fibrous tissue, is extremely difficult and infinitely more so than primary implantation. Kermanner, considering the difficulties of secondary implantation, advises nephrectomy whenever a ureterovaginal fistula fails to heal spontaneously in three months.

The difficulty and frequent failure of secondary implantation prompts the report of a case with bilateral ureterovaginal fistula cured by implantation of both ureters into the bladder.

Alice B., aged forty-two years, was admitted Sept. 1, 1933. (Hospital No. II 9638.) The patient's one pregnancy had ended in spontaneous miscarriage. During February, 1933, she noticed a bloody vaginal discharge between otherwise normal menstruations. Diagnostic curettage performed February 5 revealed cancer of the cervix. Following local treatment with radium, abdominal radical extirpation of the uterus was performed April 10, 1933. After the operation the patient noticed considerable drainage of urine through the vagina, although she was able to void. Except for this condition she felt well and had gained in weight just prior to her entrance into the hospital, her weight being 104½ pounds.

Examination on admission to the University Hospital revealed a fair general condition and no organic disease. The vagina was long, soft, and without infiltration of vaginal stump or paravaginal tissue. Rectal exploration gave no evidence of a local return. After exposing the vaginal fornix, urine could be seen draining through the fistula into the vagina. The bladder was filled with a solution of indigocarmine, but no colored fluid drained into the vagina, nor was the amount of drainage increased. The diagnosis of ureterovaginal fistula was made. After having given the patient a good rest and daily sitz baths for ten days, cystoscopy was performed on September 11 which revealed the following findings: capacity of bladder and mucosa normal. The left ureter showed rhythmical contractions expelling clear urine, and was catheterized without difficulty. The right ureteral ostium was contracted and a catheter could be inserted for only 3 to 5 mm. Four minutes following the intravenous injection of indigocarmine, clouds of blue urine were passed through the left ostium, while on the right a scarcely perceptible amount of stained urine appeared only at long intervals. After another attempt to introduce a catheter into the



right ureter, the secretion on this side stopped entirely. The exposure of the vaginal fornix now showed definitely the opening of the fistula, through which the stained urine was spurting at rhythmical intervals. A catheter could easily be inserted through the fistula into the ureter and pushed up into the pelvis of the right kidney. The intravenous pyelogram showed a perfectly normal condition of both kidneys. From these findings it was concluded that there was a fistula of the right ureter, located near its insertion into the bladder, and, therefore, its implantation was considered. With the consent of the patient, laparotomy was performed under spinal anesthesia the following day.

Operation September 12, 1933: After having inserted a catheter into the right ureter from the vagina, a median incision was made through the old scar, and many adhesions of the bowels to the peritoneum separated. During the dissection of a loop of bowel, which was extensively attached to the vaginal stump by dense scar tissue, the vagina was opened and the catheter exposed. The peritoneum was split and the ureter dissected and found to be enlarged to the size of a little finger. The enlargement was not caused by dilatation, but by a firm edema of the wall of the ureter. After sufficient mobilization the ureter was split for a few millimeters and each flap caught with a suture. A clamp was introduced into the bladder through the urethra in order to locate the most suitable place for implantation, the wall incised on the tip of the instrument, the end of the two "traction" sutures caught by the forceps, and the ureter pulled into the bladder. The margins of the opening of the bladder were pulled up and fastened wall to wall to the ureter by fine sutures. The peritoneal incision was closed by interrupted sutures, whereby the wall of the bladder was lifted up in order to eliminate as far as possible any tension, and the abdomen closed in layers. Finally the "traction" sutures, which had not been knotted, were pulled out and a retention catheter was inserted into the bladder.

The postoperative course was uneventful. The patient was up on the ninth day and the retention catheter removed on the tenth postoperative day. Sixteen days following the operation the patient was discharged. Examination did not reveal any drainage of urine into the vagina, although a moderate secretion from the granulating vaginal fornix had a urine-like odor. On October 19, twenty days following discharge, the patient was readmitted, complaining that she had been losing urine through the vagina since the second day after her return home, although considerably less than before the operation.

Inspection of the vaginal fornix revealed a granulating sinus exuding some moisture with urinary odor, but no dribbling or spurting of urine. Cystoscopy showed that at the place of implantation one flap of the ureter had retracted and slipped out of the bladder, and only one was protruding into the bladder. The part of the wall of the bladder to which this flap was tightly fixed was retracting and bulging vigorously at rhythmical intervals.

On the pyelogram a definite though moderate hydronephrosis of the formerly normal right kidney was noted. As the ureter was evidently in close connection with the wall of the bladder, another attempt at implantation seemed justified. Laparotomy was performed under spinal anesthesia on November 6 along the old incision, whereby the scarred tissue was excised. After separation of many adhesions the ureter was dissected and found to be slightly dilated, but without any edema of its wall, and fixed to the wall of the bladder. The ureter was severed and split, but this time both flaps were fixed to the wall of the bladder by sutures, according to Sampson, in order to prevent another slipping of the ureter. A retention catheter was inserted into the bladder, and the abdomen closed in the ordinary way. The postoperative course was uneventful, but in order to be sure of the result, the patient was kept in the hospital for twenty days. Six weeks following her discharge the patient returned with a letter from her physician, stating that she had been losing

urine since shortly after discharge in the same amount as before the first operation. She and her husband were determined to have the kidney removed.

The general condition of the patient when she was readmitted on Jan. 8, 1934, had considerably improved, and she had gained fifteen pounds in weight. Inspection of the vaginal fornix gave evidence that the fistula had shrunk, but not entirely closed. No drainage of urine could be seen, but a small amount seemed to have oozed into the vagina during examination. Bilateral pyelograms disclosed that the pelves of the right kidney which had been found dilated prior to the second operation, had become normal.

Studies with the injection of indigocarmine gave evidence of normal function of both ureters and kidneys. The introduction of a catheter into the right ureter failed to keep the patient dry, while the drainage was stopped entirely by catheterizing the left ureter.

Thus it became clear that from the beginning there had been a bilateral ureterovaginal fistula draining through one opening in the right fornix of the vagina. Further studies showed that in order to keep the patient dry it was sufficient to insert the catheter only 2 to 3 cm. into the left ureter. Another pyelogram confirmed the conclusion that the opening in the ureter was near its vesical insertion, so that its implantation into the bladder could be considered. As almost all the urine from the left kidney was found to be emptying into the bladder during this and the previous cystoscopic examinations, no injury of the left ureter had ever been suspected, and it seemed likely that the fistula was a very small one. Knowing that such fine "hair-fistulas" occasionally close spontaneously if kept entirely out of function over a period of time, a catheter was inserted into the left ureter and kept in place for two weeks. Although the patient felt well during this time and was dry, she began to lose urine as soon as the catheter was removed. A third operation was therefore performed on Feb. 6, 1934, under spinal anesthesia after a catheter had been passed into the left ureter. After having separated many adhesions, the peritoneum was split and the left ureter was dissected. The ureter was found moderately dilated and considerably thickened by hard edema, and near its vesical end it was embedded in scar tissue. The ureter was severed near the bladder, split, and pulled into the bladder, where both flaps were fixed to the wall of the bladder by fine catgut sutures. The margins of the bladder incision were pulled upward and fixed to the periureteral tissue by several sutures. After insertion of a retention catheter into the bladder, the abdomen was closed in layers. The postoperative course was uneventful. The retention catheter was removed on the eleventh, and the patient allowed up on the fifteenth day. She was discharged on the seventeenth postoperative day without any leakage of urine.

Since discharge the patient has been treated several times for mild cystitis, but has remained dry. A thorough cystoscopic examination and pyelogram taken five months later showed normal function of both kidneys and ureters.

Although the patient was in perfect health, two possible complications had to be kept in mind, a return of the cancer and the development of a stricture of the right ureter. The ureter, being markedly shortened by the primary injury and the two implantations, was under a permanent axial tension effecting a reduction of its lumen. Under these circumstances even a moderate shrinking of scar tissue was likely to result in a stricture. This actually happened thirteen months following the implantation, when the patient developed an acute attack of hydronephrosis on the right side, which was relieved by introducing a fine catheter into the right ureter. Various attempts to dilate the stricture were unsuccessful, and the right kidney had to be removed.

# THE INCIDENCE OF PUERPERAL INFECTION IN PATIENTS DELIVERED IN THE HOSPITAL AS COMPARED TO PATIENTS DELIVERED AT HOME

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FOR many years there has been considerable discussion concerning the incidence of puerperal infection following delivery in the home as contrasted with the lying-in hospital. There have been frequent statements made in the literature to the effect that the average obstetric patient is safer at home than in the hospital, and the following study has been undertaken in an effort to compare the incidence of puerperal infection in institutional and domiciliary practice.

At the outset it was felt that there were two factors which had to be considered in order to present comparable figures: first, the large number of late admissions of abnormal and neglected patients to a hospital service with its resulting high incidence of operative deliveries and its attendant increase in morbidity; and second, the relative lack of postpartum supervision of patients delivered in the home as compared to those in the hospital.

In consideration of the first factor we have included as a control group the cases of multiparas who were delivered spontaneously of viable children without operative induction by bag or bougie on the Hospital Service of the Johns Hopkins Hospital between May 1, 1932, and April 30, 1934, inclusive, and have compared them to multiparas delivered in like manner by the Outside Service during the same period of time. Concerning the second factor, it has long been noted that mild cases of puerperal infection are demonstrable by fever only in the afternoon and evening, and it has been thought that many of them have been missed on the Outside Service owing to the fact that the nurse in making her postpartum visits was able to record only one temperature reading per day, and this usually between the hours of eight and eleven in the morning. Therefore, in order to obtain closer supervision of the cases delivered at home during the years 1933 and 1934, temperatures have been taken every four hours from eight in the morning to eight at night in the following manner: Four thermometers were left at each house in separate envelopes marked with the appropriate hour. The patient was instructed to place each in her mouth for five minutes at the proper time and then to replace each in its envelope for the nurse to read on her morning rounds. Patients were cautioned not to drink hot liquids before taking the temperature and to keep the thermometers

in a cool place when not in use. If fever was noted by the nurse, the externe was immediately notified and the cause investigated.

The criterion employed for a febrile puerperium is that of the Obstetrical Service of the Johns Hopkins Hospital, namely, two elevations of temperature to 100.4° F. or higher on two or more days of the puerperium not necessarily consecutive, and excluding the first twenty-four hours after delivery. A diagnosis of puerperal infection has only been made in those cases in which the fever could not be adequately explained on a basis of pyelitis, upper respiratory infection, mastitis, or other causes, and in whom there was some direct evidence of uterine involvement as shown by abdominal pain and tenderness, foul lochia, and other signs. No patients were included who had been attended during pregnancy or labor by midwives or outside physicians.

Finally, we wish to state that the patients in the series, both hospital and home, comprise material from the tenement district of a large city and are about equally divided between whites and blacks. We, therefore, feel that while this series of cases may not be comparable to another from a different city or class of individuals, they are certainly comparable to each other.

TABLE I. HOSPITAL CASES

*May 1, 1932—April 30, 1933*

Multiparas delivered spontaneously	340
Cases of puerperal infection	15
Incidence of puerperal infection	4.4%
Febrile, other causes	10

*May 1, 1933—April 30, 1934*

Multiparas delivered spontaneously	365
Cases of puerperal infection	18
Incidence of puerperal infection	4.9%
Febrile, other causes	10

Table I shows the incidence of cases of puerperal infection among 705 normal women delivered at the Johns Hopkins Hospital during a period of two consecutive years, and it should be pointed out that there is only a very slight difference (0.5 per cent) between one year and the other.

TABLE II. OUTSIDE CASES

*May 1, 1932—April 30, 1933*

Multiparas delivered spontaneously	479
Cases of puerperal infection	4
Incidence of puerperal infection	0.8%
Febrile, other causes	5

*May 1, 1933—April 30, 1934*

Multiparas delivered spontaneously	510
Cases of puerperal infection	43
Incidence of puerperal infection	8.4%
Febrile, other causes	5

Table II shows the incidence of puerperal infection as recorded on the Outside Service during the same two-year period and includes 989 cases.

During the years 1932 and 1933, there was but one temperature reading per day taken by the nurse on her morning rounds, while during 1933 and 1934, temperatures every four hours were obtained as described above. The increase in the incidence of puerperal infection from 0.8 per cent to 8.4 per cent is entirely the result of the closer supervision of cases during the second year, since only the nurses' record of morning temperatures had been used, there would have been four rather than forty-three cases diagnosed, a figure identical with that of 1932 and 1933.

That the general character of puerperal infection did not change in the locality in question from one year to the next is suggested by the fact that during each year there were three cases on the Outside Service considered sufficiently severe to warrant transfer to the Hospital, and also by the fact that the average duration of fever for both years as well as its maximum height among the Hospital cases was approximately the same. A careful study of the comparative severity of the infections occurring in the hospital and the home revealed nothing of significance. The height of the temperatures and their duration was about the same in both series of cases. Of the cases included in this study, there was one death on the Hospital Service which followed a prolonged labor of forty-five hours and severe perineal lacerations with an ensuing streptococcus septicemia, and one death on the Outside Service which was the direct result of a fulminating eclampsia. From the similarity of the character of the infections occurring in the two series and from the definitely increased frequency of puerperal infection among patients delivered in the home (8.4 per cent as against 4.69 per cent), we believe that hospitalization of the lying-in woman is an important factor toward her well-being.

#### CONCLUSIONS

1. The incidence of puerperal infection was almost twice as great in a series of normal women delivered in the home as in a comparative group delivered in the hospital.
2. No difference in the severity of the infection could be elicited between the two groups.
3. This study would seem to indicate that in the modern maternity hospital the patient has a better chance of escaping infection than in the home.

## INTESTINAL OBSTRUCTION COMPLICATING PREGNANCY

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THE literature of recent years reveals a comparatively small number of references to intestinal obstruction in pregnancy. The majority of cases reported apparently terminated in premature labor with loss of the child. In many of the cases the mothers were also sacrificed.

DeLee mentions it as a rare complication which may be due to the same causes capable of producing it outside of pregnancy. Curtis in a recent work devotes a small paragraph to the condition and concurs in DeLee's opinion. The greater number of cases reported appear to be the result of abnormal adhesions of the intestines to the uterus, the latter organ in its growth dragging on the intestines and producing complete obstruction. All of the authors are of the opinion that recognition of intestinal obstruction constitutes an imperative indication for surgery and without needless delay. In the majority of cases this is to be followed by induction of labor or such other operative measures as the situation demands.

The case reported herewith appears to be of unusual interest because of the many incidental factors and also because of the fact that after surgical interference for the relief of the obstruction, the pregnancy was successfully carried on and the mother normally delivered at term.

Mrs. B. H., aged twenty-two years, white, nullipara, was first seen on June 10, 1932. She had been married four months. Her previous history was irrelevant. She had had no serious illnesses and no operations. Her menstruation had begun at twelve years of age and had always been of a twenty-eight-day type. No dysmenorrhea.

On the fifteenth of April she menstruated normally. Two weeks following this she passed a small amount of blood, the flow lasting two days. Several days later she had a slight cramplike pain in the lower abdomen which disappeared in a short while. There was no nausea; no unusual soreness of the breasts. She did not menstruate in May. On June 6 after flowing slightly for four or five days she suddenly had sharp pains in the right lower abdomen. This lasted for several hours, then disappeared. She did not faint. On June 10 she had another attack of pain, not as severe, however, as the preceding one and she felt rather faint. I was called to see her for the first time on this date.

Examination revealed a well-developed and nourished female who was rather pale. The general examination was essentially negative. Blood pressure was 110/80, pulse 100, and temperature 98.4°. The abdomen was markedly rigid and tender to pressure over the entire right lower quadrant. Pelvic examination revealed a normal nulliparous introitus. The cervix was soft, a moderate amount of bright red blood presenting. The uterus was slightly enlarged, anteflexed, soft and partly fixed. There was a mass about the size of a lemon in the right tuboovarian region; this was extremely tender. There was an impression of bogginess in the culdesac. Diagnosis of ruptured ectopic pregnancy was made and the patient was admitted to St. John's Hospital.

Operation under spinal anesthesia of 150 mg. of novocaine. A midline incision was made. The peritoneal cavity contained free blood. The right tube, markedly distended, was the seat of laceration at the isthmus. The placenta and embryo had been expelled from the tube and were lying on the anterior surface of the round ligament, and it appeared that the placenta had begun to attach itself at this

point. Placenta and ovum were carefully removed. The broad ligament was clamped and the right tube including its interstitial portion was removed. A simple cyst on the right ovary was punctured. The left tube and ovary were normal. The patient being in good condition, the appendix was removed in the usual manner and the abdomen closed without drainage. Convalescence was uneventful. Examination two months after operation revealed the pelvis in apparently good condition.

*Subsequent History.*—In May, 1933, the patient presented herself at the office, stating that she was anxious to become pregnant. She had used no contraceptives for three months. Examination revealed the pelvis apparently normal. Carbon dioxide tubal insufflation by the Rubin method was performed. After two attempts using a maximum pressure of 200 mg. the gas entered at 140 mg. and more rapidly at a lower level. She had the typical shoulder pain. The June period was normal. On July 3 she menstruated slightly for two days. A few days later she had a slight pain in the left side. At this time there was some soreness of the breasts. Examination eliciting no pathology she was advised to keep in touch with the office, reporting again in a few days. On July 16 she returned, the slight intermittent bleeding persisting at this time, and she had had slight cramping pains at times in the left side. The uterus appeared slightly enlarged and there was definite thickening about the left uterine cornu; this was quite tender. It appeared that I might be dealing with another ectopic or possibly cornual pregnancy. She was kept under observation. A few days later, following a severe attack of cramps she passed a large clot which, however, was not saved for examination and her symptoms immediately subsided. This would suggest that she might have had an early abortion.

On Jan. 4, 1934, she presented herself at the office complaining of some nausea and soreness of the breasts. Her last menstruation was Nov. 7, 1933. Examination revealed the uterus size of six weeks' pregnancy. The adnexa were apparently normal. The pelvic measurements taken at this time were found to be within normal limits. Term was estimated at about Aug. 14, 1934.

In March she complained of slight increase in nausea and of some cramplike pains in the lower abdomen. The bowels were acting normally and the examination was essentially negative. On April 29 she had what she believed was indigestion. She had a severe pain in the left lower abdomen and was nauseated. Taking on her own initiative, doses of soda followed by enemas, she had several good bowel movements, but continued to have cramplike pains.

Examination at this time revealed rather marked uterine contractions, and it was feared that she might miscarry. No vaginal examination was made. There was no bleeding. She was put at rest and the symptoms subsided after two doses of morphine. For several days she felt very well. On May 1 she vomited several times, was markedly distended; stated that her bowels had not moved for two days. Enemas and the other methods employed being ineffectual, it was decided that complete intestinal obstruction was present and operation was decided on. She was removed to St. John's Hospital.

At operation under spinal anesthesia a left rectus incision at about the level of the umbilicus was made. This point was selected because of the location of the pain and the probability that nothing would be done but an ileostomy. This subsequently proved to be an error. On opening the peritoneal cavity free fluid presented. The patient appearing to be in good condition and no obstruction being noted on the left side, the hand was introduced further and the terminal ileum was found densely adherent to the uterus at the point originally occupied by the right tube. In its growth the uterus had pulled on the intestines, producing an acute angulation. The adhesions were freed and two small injuries to the intestinal serosa were repaired. As the intestines appeared to empty themselves spontaneously one ampule of amphetamine was introduced into the peritoneal cavity and the abdomen was closed

without drainage. Gastric lavage was performed on the table, and it was noted that the patient also passed a large amount of gas and liquid stool.

Preoperative and postoperative treatment consisted of frequent intravenous injections of hypertonic saline solution to combat the loss of chlorides; solutions of glucose being given simultaneously. The patient did well until the third postoperative day when there occurred an acute gastric dilatation, and she appeared acutely ill. Gastric lavage through a nasal tube, which was allowed to remain in situ for forty-eight hours, was performed. There was no recurrence of symptoms. On May 8 the bowels moved spontaneously several times and her condition thereafter was quite satisfactory. During this period the child was quite active and no abnormal uterine contractions were noted. She left the hospital in good condition on the twelfth postoperative day. The abdominal wound was well healed.

On June 1 examination revealed the child in the vertex, growing normally. On July 5 she had rather severe Braxton-Hicks contractions which, however, subsided after a small dose of opiate. On July 18 contractions again started and as labor appeared imminent she was admitted to the hospital. The child was in vertex R.O.A. Cervix was rather thick, and dilatation one finger. That evening progress being rather slow, contractions poor and irregular, the cervix dilated three fingers, the membranes were ruptured instrumentally. Contractions were further stimulated with three minum doses of pituitrin given at half-hour intervals. When dilatation had reached  $3\frac{1}{2}$  fingers, nitrous oxide anesthesia was administered, progress from then on being fairly rapid. After the head had been expelled from the cervix, forceps were applied after a deep lateral episiotomy and a female child weighing 5 pounds 4 ounces was delivered in R.O.A. Child was in good condition. Placenta and membranes were expelled intact. Episiotomy was repaired. There was no abnormal bleeding. As the mother appeared to be slightly dehydrated, 500 c.c. of 5 per cent glucose was given intravenously. Puerperium was uneventful and the patient left the hospital on the tenth day.

Final examination at the end of six weeks revealed the abdominal wounds well healed. The cervix was normal and the perineum was well healed. The uterus was in good position. The breasts were in good condition, no attempt having been made to nurse the baby.

This case appears to be worthy of comment because of the many factors that were brought into play during the time this patient was under my care. Of interest is the fact that pregnancy followed tubal insufflation; this therapeutic and diagnostic procedure having undoubtedly freed some fine adhesions probably resultant of the original operation.

Spinal anesthesia favored the contraction of the intestines after the adhesions were freed. This apparently forestalled the necessity of intestinal drainage by ileostomy. Amphetamine was used following freeing of adhesions in an attempt based on recent clinical reports to prevent their recurrence.

The duodenal tube proved a life-saving measure in the treatment of and prevention of recurrence of gastric dilatation.

With full knowledge of the part played by the unknown factor "luck" in the management of this case it was, however, impressed on me more than ever that the so-called obstetric specialist should be more than a mere midwife, but be trained in and competent to perform such abdominal surgery as can occur as a complicating factor during the course of any pregnancy.



## MODIFICATIONS OF THE ASCHHEIM-ZONDEK REACTIONS WITH ABORTION

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**D**EVIATIONS from the standard changes noted in the ovaries of rats used in the Aschheim-Zondek test, namely, modifications in the intensity or even the absence grossly of one or more of the results termed Reactions I, II, and III, accompanied by an estrous hypertrophy of the uterus may occur so regularly with certain complications of pregnancy that they become important criteria in diagnosis.

When the report by Jeffcoat<sup>1</sup> in 1932 appeared describing these modifications of the Aschheim-Zondek reactions with abortion, independently, the same variations had come to my notice and had been correlated with abortion or impending abortion. Jeffcoat's original description, therefore, is confirmed by my observations.

For each test three immature female white rats, litter mates, twenty-five to thirty days old, were used. Two cubic centimeters of cleanly collected urine was injected intraperitoneally into two rats, twice daily for two days, the third and largest rat being used for a control. Forty-eight to seventy-two hours after the last injection all of the rats were killed and the genitalia examined. In a positive test the results were clear and all three reactions were present grossly in the ovary. When in doubt, the ovaries were removed, one was pressed between glass slides and examined with direct daylight or under the microscope for Reactions I and III. The other ovary after washing was cleared in glycerin overnight in order to bring out Reaction II. The enlargement of the uterus was always apparent grossly.

The urine of women aborting or with impending abortion caused much milder changes in the ovaries of immature rats than occurred in the usual positive Aschheim-Zondek test. The ovaries while slightly lobulated (mulberry shape) were pale. Ripening follicles and poorly formed corpora lutea were usually visible, while corpora hemorrhagica, when present, required magnification. These results would be expressed as follows: Reaction I, +++ to ++++; Reaction II, 0 to +; Reaction III, + to ++. In contrast with the mild reaction of the ovaries, the uterus was enlarged and hyperemic as in estrus. The diameter of the horns often equaled or even exceeded that of the small bowel in the rat.

Representative results are collected in Table I.

Patients 1 and 2 are typical of impending abortion. Bleeding started in Patient 1 a few days after the results in the rats were known, and in Patient 2, four days after the first sample of urine was injected. Abortion followed. Abortion in the other three patients was incomplete. Three separate tests were made on the urine of the third patient, each with the modified reaction as described. An attempt to induce abortion had been made by this patient before she came to the hospital, but this was not admitted until after the third test had been completed. Without this information ectopic gestation had been considered. Sixteen days of observation,

however, between the first and second tests eliminated this possibility. The patient had bled about two months, when the last test was made and chorionepithelioma or hydatid mole had been considered, but the mildness of the ovarian reaction in each of the three tests excluded this. The diagnosis of incomplete abortion in the last two patients of the table was confirmed by operation and microscopic study. The modified reaction in the rats was the only indication of abortion. The clinical

TABLE I

NO.	METRROR-RHAGIA	CLINICAL DIAGNOSIS	ESTIMATED PERIOD OF PREGNANCY	OUTCOME PREDICTED	REMARKS
1	None	Pregnancy ?	2 mo.	Impending abortion	Bleeding started several days after the results of the rat test were known.
2	None	Pregnancy ?	1½ mo.	Impending abortion	Bleeding started the day after the rats were examined.
3	Some spotting	Ectopic pregnancy ? Abortion ?	2 mo.	Incomplete abortion	The results of three tests (4/4/34, 4/20/34, and 5/24/34) were alike. The statement of an attempted induced abortion was obtained after the last test. Patient bled continuously for six weeks while under observation.
4	2 mo.	Ectopic pregnancy ?	2½-3 mo.	Incomplete abortion	Chorionic villi were in tissues curetted from the uterus.
5	2 mo.	Right ectopic pregnancy ?	3-4 mo.	Incomplete abortion	Chorionic villi were in tissues curetted from the uterus.

history, symptoms, and physical examination of both suggested an ectopic pregnancy, but surgical operations demonstrated no changes of the fallopian tubes, and tissues obtained from the uterus by curettage contained chorionic villi.

Only one pregnancy was observed which did not abort when an "abortion" reaction was obtained. Three weeks before the test was made this patient had slight metrorrhagia, too early for her regular period. Two days after the urine was collected there was more hemorrhage, but no fetal tissues were recovered. After ten weeks she obviously was pregnant.

The end-results and the rat reactions obtained with urine from three other patients were confusing. One ended in term delivery, the second was progressing normally in pregnancy when last seen, and the third was not pregnant. The reactions in rats produced by the urine of these three women were alike, but different from either the usual "positive" Aschheim-Zondek or the modified reaction associated with abortion. The three reactions in the ovaries simulated those of the "positive" Aschheim-Zondek test, but the uterus was markedly enlarged as the "abortion" reaction. The patient who delivered at term had bled for the first two and a half months of pregnancy, and abortion was anticipated. The patient not pregnant was approaching the menopause and had not menstruated for five months.

The implication has been made that the urine of these women with abortion contained a large quantity of estrin. This view conflicts with Bland's,<sup>2</sup> who believed that estrin production diminishes with the death of the fetus. The tissue recovered from Patients 4 and 5

of the table were only small placental residues, but the urine contained much estrin judging by the hypertrophy of the uterus in the rats. The urine of Mazer and Goldstein's<sup>3</sup> patient gave a positive estrin test after a dead fetus had been carried for four months. Jeffcoat not only considered that a large amount of estrin was present in the urine of patients with incomplete abortion but thought that the amount exceeded the anterior pituitary hormone. He concluded that estrin counterbalances the maturity producing effect of the gonad-stimulating hormone in producing the modified reactions of the ovary in patients with impending or incomplete abortion. The experiments of Leonard,<sup>4</sup> Allen,<sup>5</sup> and Dahlberg<sup>6</sup> seem to confirm this view.

#### SUMMARY

1. Abortion impending or incomplete may be diagnosed by the modified reactions of the Aschheim-Zondek test in the ovaries of white female rats. These may be expressed as follows: Reaction I, +++ to ++++; Reaction II, 0 to +; Reaction III, + to ++. Accompanying these modifications is an estrous hypertrophy of the uterus.

2. All pregnant women but one, whose urine produced this reaction in routine tests, aborted.

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Urine from 51 women in the last two months of pregnancy was injected intravenously into the same number of male rabbits of approximately three months of age, from several breeds. Gross and microscopic examination of the testes removed before and after treatment gave the following results: (1) the urine injected had no appreciable effect upon the gross appearance of the testes, the seminiferous tubules, or upon the number of different kinds of germinal epithelial cells; (2) In an insignificant number of instances the treatment may have initiated or increased spermatogenetic activity; (3) The testes of animals treated with urine from women who later were found to have given birth to female children exhibited the same microscopic picture as those testes from animals which were treated with urine from women who had later given birth to male children. From these observations it is concluded that the urine from pregnant women does not offer a means of predicting the sex of the unborn child by the rabbit testis reaction.

J. THORNWELL WITHERSPOON.

## PURPURA HEMORRHAGICA IN PREGNANCY

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THAT purpura hemorrhagica is infrequent in pregnancy is evidenced by the fact that up to 1925 only 47 cases had been reported in the literature. The first was that of Barnes<sup>1</sup> in 1867, the patient dying the day after delivery. Rushmore<sup>2</sup> in 1925 reviewed the 47 reported cases with some interesting observations. It seems more frequent in multiparas. In this series there were 32 multiparas, 7 primiparas, and 8 in whom the parity was not given. The time of its appearance is predominantly the second half of pregnancy. In Rushmore's 47 patients, 43 developed after four and one-half months; the remaining 4 in the first half of pregnancy, the earliest case appearing in the second month.

Philip Liebling<sup>3</sup> reported one case in 1926; Hottenstein and Klingman<sup>4</sup> one in 1927; in 1932 M. Palombekki<sup>5</sup> one case, and G. Teasuro<sup>6</sup> two cases; F. Conti<sup>7</sup> one case; and P. Henriets one case, in 1933. Of these seven cases three terminated fatally.

The case here reported occurred on the Obstetrical Service of the Roper Hospital, May, 1934.

Mary B., Case 76095, a colored woman thirty-five years of age, was admitted on May 11, 1934. Her chief complaint was bleeding.

On the morning of the day of admission the patient began to have bleeding from her mouth (spitting bright red blood) and to "feel bad all over." She had dark spots before her eyes and dull pain in the lower part of her abdomen. About 1 P.M. she noted vaginal bleeding. She called a doctor but left for the hospital before his arrival, and had a sudden gush of bright red blood from the vagina as she was leaving home. Bleeding continued, but was less profuse at the time of admission than before. She vomited greenish fluid several times during the day, with no appearance of blood. The patient was pregnant, approaching full term, her last menstrual period having occurred in August, 1933. This pregnancy, her ninth, had been subjectively normal, as were all her other pregnancies. She had had seven living children and one stillbirth.

The patient was a well-nourished negress, in mild degree of shock. Her temperature was 99.8° F., pulse 116, weak and of poor volume. The blood pressure was 106/80. She had a small laceration of the mucous membrane of the tongue; gravid uterus about the ninth month, in a state of hypertonic muscular tension, without rhythmic contractions; and signs of continuous bleeding from the mouth and the vagina. The bleeding from the mouth did not appear to be due to the small laceration. Fetal heart sounds could not be heard. A catheterized specimen of urine contained a large amount of blood, grossly evident.

Expectoration of blood-tinged saliva, and vaginal bleeding with some spurts of bright red blood, continued until the day after admission. Vomiting recurred. Bleeding diminished about fifteen hours after she was admitted. At this time (7:30 A.M. on May 12) the patient complained of labor pains, but the rhythm of uterine contractions was masked by the tonic state of the uterus. The morning after admission she was delivered of a full-term, stillborn male infant. The placenta,

which was delivered intact, was of a leathery consistency. Moderate bleeding followed delivery. No further abnormal bleeding occurred during that day nor subsequently. The patient's later course was uneventful, but for a continued state of anemia. No subjective symptoms referable to this were encountered, nor any referable to nephritis or renal insufficiency. She was discharged on June 16, 1934.

*Treatment.*—At 5:15 P.M. on May 11, thirty minutes after admission, 2 c.c. of horse serum were administered intramuscularly, followed thirty minutes later by an additional 10 c.c. This was followed by 500 c.c. of 10 per cent glucose intravenously. At 10:15 P.M. (within six hours after admission), with bleeding continuing, an x-ray treatment was given. At 11:45 P.M. 10 c.c. of antivenin were administered. Morphine and atropine were given before delivery, and pituitrin after the third stage. On the day of delivery a transfusion of 440 c.c. of whole blood was given. The other medications consisted in ergot, postpartum; iron with copper and arsenic; and sodium perborate as mouth wash.

*Laboratory Findings.*—These consisted notably in hematuria, thrombocytopenia, changes in the erythrocytes characterizing a moderately hypochromic and microcytic anemia, and temporary retention of nitrogen. Smears from the mouth showed fusiform bacilli and spirochetes of Vincent.

TABLE I. LABORATORY FINDINGS IN PURPURA HEMORRHAGICA (CASE 76095)

DATE	5/11/34	5/12/34	5/13/34	5/16/34	6/7/34	11/15/34
Platelets	33,000	52,000 (12 hours after irradiation of spleen)	246,000 (18 hours after transfusion. 36 hours after irradiation)	194,000	130,000	237,000
Bleeding time	More than 30 minutes. (Bleeding stopped by pressure at 30 min.)	20 minutes				
Coagulation time	5½ minutes	5 minutes				
Hemoglobin	84%	43%		43%		67%
Erythrocytes				2.72 million		4.79 million
Reticulo-cytes					6%	
Total leuco-cytes	21,000		6,350		3,800	
Polymorpho-nuclears	72%		82%		70%	

In addition to these characteristic features of thrombocytopenic purpura, our case manifested bleeding into the urinary tract, which is apparently rare. On admission a catheterized specimen of urine contained a large amount of blood, too large for the significant interpretation of other findings in that specimen. The next catheterized specimen, obtained six days later, contained only a few blood cells on microscopic examination. At this time, five days after delivery and after the cessation of spontaneous bleeding, with no signs or symptoms to suggest renal failure, a blood chemical analysis showed marked nitrogen retention, the urea nitrogen being 152 mg., the creatinine 20.4 mg., figures which, in a chronic case of renal insufficiency with nitrogen retention, would foretell a certain and early fatal termination. Successive

blood chemical analysis showed steadily decreasing urea nitrogen and creatinine, the figures sixteen days later (June 4) being 66 mg. for urea nitrogen and 5 for creatinine, and continuing to fall. A phenolsulphonephthalein kidney function test at this time (June 8) showed first hour excretion 5 per cent, second hour 2½ per cent. Before discharge from the hospital, five weeks after admission, the urea nitrogen was 29 and kidney function by urea clearance test was 13 per cent of normal. Her apparent tendency to steady improvement was further demonstrated by a kidney function test (urea clearance) made on November 15, five months after the previous one, showing that the blood urea nitrogen had reached the upper normal level of 18 mg., although the clearance was still below normal, being 30 per cent. A search of the literature has revealed only five patients in whom hematuria was noted; of these, four died and records of autopsies are available on two. In only one case were the findings and pathology described such as we believe to be illustrated by our case. In the case reported by Tesauro<sup>6</sup> death resulted from intracranial hemorrhage, and autopsy revealed also the fact that the capsules of the kidney glomeruli were filled with blood. Such a lesion would account for retention of nitrogenous products by mechanical interference with glomerular function, without necessarily inflicting permanent injury upon the glomerular tissue.

Adding to the 44 cases previously reported the 8 here collected in which the final results are known, we have a total of 52 cases with 29 deaths, a mortality of 55.7 per cent.

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Schmid, H. H.: Artificial Endometriosis, Arch. f. Gynäk. 155: 217, 1933.

Schmid transplanted uterine mucosa into the vaginal wall, thus producing an artificial endometriosis since all of the transplants grew. The author did this in 19 women and produced a regular menstruation with external discharge in all. This makes it possible to produce regular menstruation in young women with functioning ovaries even after the uterus has been removed. The value of this procedure is entirely psychic but can be used to prevent the psychic depressions which are found in many young women who have undergone hysterectomy.

RALPH A. REIS.

Albrecht, H.: Malignancy of Rectouterine Endometriosis—Radical Surgery or Radiation. Arch. f. Gynäk. 155: 74, 1933.

The author collected 359 cases of rectouterine endometriosis from the world literature and from his analysis concludes that radical surgery is not only dangerous but also unsatisfactory in that much diseased tissue is left in situ. Since endometriosis is directly dependant upon ovarian function, simple ovarian destruction is sufficient. This may be accomplished by bilateral ovarian extirpation but can be done in a simpler and safer manner by radiation, either with radium or x-ray. All that is necessary to cure this condition is the production of an artificial menopause.

RALPH A. REIS.

## TWIN PREGNANCY WITH ONE LIVING FULL-TERM CHILD AND ONE FETUS PAPYRACEOUS

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MRS. M. B., Mexican, aged twenty-four, was admitted to Golden State Hospital Sept. 30, 1933, in labor. Married three years, the patient had a living male child apparently normal in every respect. The present gestation dated to the last menstrual period Dec. 23, 1932, prior to which time the menses had been quite regular except for occasional irregularity in the form of prolonged intermenstrual periods since the birth of the first child. Before the first pregnancy her menses had been regular, of the twenty-eight-day type, lasting four days, and not painful. There had been no miscarriages. During the first six or seven weeks of the latter pregnancy the patient had experienced dull dragging pain in the right upper quadrant of the abdomen and in the right flank. She had noted in the latter months of gestation absence of the feeling of fullness in the pelvic region which she had noted with the first child. She had attended the prenatal clinic for the first time ten days before coming to this hospital. On this occasion she was not informed of any unusual findings on examination if such had been encountered. Pains had begun at 11 A.M. on Sept. 29, 1933, were not severe, and occurred every ten to twelve minutes.

The general physical condition was good. The abdomen was slightly pendulous, flaccid, and presented striae but no scars. There was about 5 cm. diastasis present. The ovoid was in the oblique, the diagonal running from the left upper quadrant to the right lower quadrant. The fetal back was toward the left side of the abdomen, the small parts were felt anterolaterally on the right side. No head was palpated in the pelvic region but it was indefinitely felt in the left upper quadrant where ballottement was elicited. The fetal heart tones were heard most distinctly to the left of the umbilicus and were 140. A diagnosis of breech presentation was made, and this was confirmed by rectal examination when the presenting part was felt high up in the pelvis and from its contour was taken to be a foot. The cervix was moderately effaced, dilated about 5 cm. and the bag of waters was intact. Preparations were made for delivery anticipating extraction of a breech-footling presentation. Before preparations were complete, the bag of waters ruptured and a large volume of liquor escaped. Soon thereafter, pains became frequent and severe and within a relatively short interval the presenting part was visible at the outlet, and on examination, proved to be a knee. The patient was anesthetized with ether and the child was extracted without difficulty. It was a male weighing 7 pounds, 3 ounces, apparently normal in every respect. The placenta separated spontaneously within ten minutes, whereupon the upper border of the uterus was palpated and presented the characteristic (hatchet) shape except in the right cornual region where a rather firm tumor mass was noted. On downward pressure over this area the placenta was delivered and thereafter the uterus was felt to be in the midline, of uniform outline and contracted. Hemorrhage was not unusual and there were no tears. Of unusual interest was a firm flattened mass inclosed in a sac on the maternal surface of the placenta and which was the first visible part of the placental mass as the latter was delivered. Through the sac the flattened mass appeared gray white in color, was about as long as the hand

from wrist to the tips of fingers, firm to hard in consistency, nonadherent to the placenta and unquestionably of fetal form. Over what was taken to be the head a small opening was made in the membranes and the fetus was expressed. The latter measured 14.5 cm. from crown to perineum and was compressed from side to side, the head symmetrically, the trunk with the (adherent) extremities, obliquely. The extremities were in a flexed attitude and fixed to the trunk by a covering of firm vernix caseosa. The ribs of the left chest wall were visible and palpable and the whole mass was firm to hard in consistency. The sac contained only a small amount of fluid and was separated from the other sac which had contained the normal fetus, by a septum made up of two layers only. On closer inspection of the dead fetus a scrotal sac was found which led to the conclusion that this was a case of monozygotic twins. The placenta was of average size, measuring 16 cm. in diameter, 13 cm. in thickness, and was of normal appearance



Fig. 1.—Photographic reproduction of x-ray of fetus papyraceous shortly after delivery showing the well-developed skeleton; also the comparative sizes of the two umbilical cords.

and consistency on both the maternal and fetal sides. There were two separate cords, the vessels of which anastomosed at the (marginal) insertion into the placenta. That of the living fetus was of average length and measured about 1.5 to 2.0 cm. in diameter. The cord of the dead fetus measured 0.5 to 0.75 cm. in diameter, and but 13.5 cm. from the placenta to the perineal region where the cord disappeared beneath the firm caseous matter which covered the trunk and extremities of the fetus. An effort was made to dissect out the vessels of both cords and to determine their interrelationship at their insertion into the placenta. It was found that arteries anastomosed with arteries, veins with veins, and there was no arteriovenous anastomosis of the larger vessels. The vessels of the cord of the dead fetus were further dissected out for the entire length of the free part of the cord, and from this point on it was possible to liberate and follow the cord. It coursed upward beneath the left thigh, the left forearm, around the neck of the fetus, and back beneath the ascending loop to the navel. In its course about the



neck of the fetus it lay in a trough-like groove. One lower extremity was dissected free and measured from thigh to knee 5 cm. and from knee to the tip of the toes 6.5 cm., the total length of the fetus approximating 25 cm. from crown to heel or about the length of the fetus in the fifth month of development. On x-ray examination the bony skeleton was found to be well developed (Fig. 1).

It is probable that in this case death of the fetus resulted from strangulation due to the cord around the neck.

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## SUPRARENAL CORTEX THERAPY IN PERNICIOUS VOMITING OF PREGNANCY

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THE purpose of presenting at this time a single case report in a subject of this kind is not an attempt to draw any conclusions, but rather a desire to stimulate obstetricians to try this form of therapy. If, as is indicated in this one case, adrenal cortex proves successful in overcoming even a few of the types of obstetric vomiting, a great advance will be accomplished.

Kemp,<sup>1, 2</sup> reported the use of adrenal cortex in 16 of his obstetric patients who were troubled with more or less mild attacks of vomiting. All but one were in the first trimester. Kemp believed that normal pregnancy was characterized by a hyperfunction of the adrenal cortex inasmuch as it was frequently found hypertrophied. He further believed that adrenal cortex insufficiency resulted in gastrointestinal disturbances of which vomiting was a prominent symptom. He therefore reasoned that some women vomited during pregnancy because their adrenal cortex did not pick up enough added function necessary for the condition. Whatever the rationale of this hypothesis proves to be, Kemp obtained complete and almost immediate freedom from vomiting in all of his treated patients. Not one of Kemp's patients had ketosis nor did any show symptoms as severe and dangerous as in our patient.

Our interest in Kemp's work was stimulated by the fact that our patient derived no relief from the conventional endocrine or other therapeutic agents. In spite of the intensive treatment accorded her for ten days in the hospital she continued to lose ground and rapidly developed such a dangerous condition that surgical intervention was indicated. Therapeutic abortion would not be sanctioned by her church. It was then decided to try intravenous suprarenal cortex (Armour's). With this medication the patient rapidly changed from a state bordering on ketotic coma to her present condition, in which she walks, eats normally, and has regained the 27 pounds lost during her stormy siege.

Mrs. B. D., aged twenty-seven, white. Appendix removed in 1926 and she had a uterine suspension in 1927. She began to menstruate at thirteen years of age, every twenty-six days for five days, the amount of which was moderate, but with severe pain. She had always been regular and had no leucorrhea. Her last period was June 8 to 13, 1934. She was married June 9, 1934. On July 21, 1934, she reported to one of us (J. M.) that she had severe nausea with persistent vomiting. She was sent home and put to bed and the conventional routine prescribed. In addition, the patient received hypodermically 2 ampoules of corpus lutein per day. This seemed

to increase her nausea and vomiting so at the end of five days it was discontinued. She was then given  $\frac{1}{2}$  gr. of thyroid (Burroughs Wellcome & Co.) q.i.d. with no improvement.

She was admitted to the Worcester Hahnemann Hospital too weak to walk. The urine showed a very marked trace of acetone and diacetic acid but no sugar. She was given 5 per cent glucose-saline solution intravenously in 1,000 c.c. doses twice on this day. Her temperature, pulse and respiration rates were 98.2°, 86, and 18. Although she took only small amounts of water by mouth, she frequently vomited large amounts of a thin, greenish-yellow fluid.

She continued to receive the intravenous therapy daily (2,000 c.c. each twenty-four hours) for the following eight days during which acetone and diacetic acid increased. She continued to vomit large amounts of fluid although only small amounts of cracked ice and tart fruit juices were taken. Even the intravenous therapy began to bring on attacks of vomiting.

She was then started on 90 gr. of bicarbonates by mouth in small divided doses. At first this made her feel better. She continued to vomit, but in lesser amounts. She still received the intravenous therapy of glucose-saline solution. As the nausea and vomiting continued the alkalies were administered rectally.

She became flushed and drowsy; there was a marked odor of acetone on her breath and a glassy stare in her eyes. At noon on that day she was given another 1,000 c.c. of glucose-saline solution intravenously to which was added, for the first time, five units of insulin. Two hours later her blood sugar was 105 mg., but there was 2 per cent sugar in her urine specimen. She was then given her first injection of an entire ampoule of suprarenal cortex (Armour's) intramuscularly. She received two more such injections of adrenal cortex during the remainder of that day. That night she was given intravenously 500 c.c. of a 10 per cent glucose-saline to which was added 20 units of insulin. The next day she reported that after the previous night's intravenous medication she had felt as if she were floating in air for a few minutes.

The following day she was again given 3 doses of the suprarenal cortex, but no insulin or glucose-saline. Although she still felt nauseated and vomited frequently, her vomitus now began to be in negligible amounts. She retained small amounts of cracked ice and tart fruit juices by mouth.

She continued to improve rapidly for the following three days, although she received only two more intravenous injections of a 10 per cent glucose-saline solution in 500 c.c. doses to which was added 30 units of insulin. These continued to make her nauseated and vomit.

At this time her general improvement was so marked that her bed was wheeled out on the sun porch. She continued to take and retain 90 gr. of bicarbonates orally. During this interval her urine showed a gradually diminishing concentration of acetone and diacetic acid, and on this day the test for diacetic acid was negative for the first time.

She began to eat and retain a fat-free diet. Her vomiting ceased entirely although her nausea was a bit more stubborn. On the thirty-first of August her urine was acetone-free for the first time. All medication had been discontinued except the intravenous adrenal cortex which she continued to get three times daily. On this day she was allowed out of bed for ten minutes. She was weighed and found to have lost 27 pounds.

She continued to regain her appetite and strength rapidly. On the second of September (ten days after the first suprarenal cortex injection) she was strong enough to go home. On this day the intravenous route was discontinued and replaced by

Armour's suprarenal cortex tablets, grains iii, three times daily. Her temperature, pulse, and respiration rates did not vary materially from those on her admission.

At present (October 8) she is at home. She eats her food ravenously, has lost all traces of nausea and continues to take adrenal cortex tablets faithfully. She now weighs 130 pounds. She has not aborted.\*

#### DISCUSSION

One may argue that insulin was used for the first time on the same day that the suprarenal cortex injections were started and that the insulin was the cause of her improvement. However, the intravenous glucose-saline-insulin injections made her sick and were, therefore, discontinued before her urine ketosis was cleared. She did not receive any insulin-glucose-saline solution for four days before her urine became acetone-free. Also, one may argue that her vomiting would have ceased spontaneously at the end of her first trimester, but she was still in her second month of pregnancy. Moreover, ketosis is a vicious cycle and is, therefore, not cleared spontaneously.

We are using it in all forms of vomiting in pregnancy and hope to publish our results as soon as our series of cases is sufficiently large. We are also using this therapy in all other forms of vomiting.

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### THE TREATMENT OF PRURITUS VULVAE WITH SUBCUTANEOUS ALCOHOL INJECTIONS

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THE therapy of pruritus vulvae in patients having other vaginal complicating factors is directed toward the eradication of the underlying condition, and all constitutional diseases must be adequately treated. In all other cases, in which no definite etiologic cause is apparent, we have found the use of perivulvar alcohol injections of great value. Such patients have usually been suffering from pruritus for a long time, and have in most instances run the gamut of local treatment, including all kinds of soothing, cooling, or anesthetic solutions or salves. Many have previously had local cautery or x-ray treatment without relief. Even surgery has been utilized occasionally. In some of these patients the itching becomes so increasingly intolerable that morphine in large doses eventually becomes necessary.

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\*This patient was delivered of a full-term male infant on March 19, 1935, both doing well.

We are reporting in this paper the results obtained in a series of fifteen cases of pruritus vulvae, treated by subcutaneous alcohol injections. The technic of the injection varied somewhat in different cases.

#### TECHNIC

As a preliminary measure, the vulva and mons veneris were shaved and cleansed, and the limits of the pruritic area marked out. The cutaneous nerve supply of the external genitals is derived from the hypogastric branch of the iliohypogastric, the inguinal branch of the ilio-inguinal, and the perineal branch of the pudic nerve. The dorsal nerve of the clitoris is also a branch of the pudic nerve. All of these nerves, except the dorsal nerve of the clitoris, penetrate the deeper structures at the outer margin of the vulva and are distributed toward the midline. Since the superficial nerve supply radiates to the midline, it suffices to inject the periphery of the pruritic area in order to cut off sensation. A separate injection is made to eliminate sensation in the dorsal nerve of the clitoris.

Under gas-oxygen anesthesia, 95 per cent ethyl alcohol is injected completely around the margin of the pruritic area. The injections may be spaced about one-quarter inch apart, a drop or two being instilled at each point as advocated by Stone in the treatment of pruritus ani,<sup>1</sup> or made as a continuous infiltration along the outer border of the vulva. The area about the clitoris is separately injected along either side of the prepuce. From 10 to 20 c.c. are required for the complete operation. More alcohol will be required for continuous infiltration than for spot injection. At the present time I personally prefer the spaced spot injections, as I believe that they accomplish the same purpose, use less alcohol, and are followed by less local reaction. Special care must be taken not to inject under the vaginal mucosa, as extensive sloughing may ensue. A reactionary swelling of the labia always appears soon after the injection. This can be partly controlled by hot applications of boric acid or Burrow's solution. The patient may be allowed out of bed in twenty-four to forty-eight hours.

#### RESULTS

In our series of fifteen patients all but two were married. The youngest was thirty and the oldest sixty-five years. Ten had had children. The duration of the itching had varied from two months to thirteen years, the average length of time being 3.7 years. Three patients had a moderate or profuse vaginal discharge. The external genitals, particularly the labia, showed evidences of scratching, excoriation, redness, and thickening. In one patient there was marked tanning and in another atrophy of the labia as a result of x-ray treatment. In twelve patients the cervix was entirely normal; one was slightly eroded and two showed nabothian cysts. The latter two patients also had profuse cervical leucorrhea. Perhaps they should not have been included in this series, inasmuch as a possible local cause for the pruritis was present. The urine and blood examination of all patients was negative. All fifteen patients had had previous medical attention. Four had novocaine injections, two had superficial cauterization, two had x-ray therapy, and one, in addition to other treatment, failed to get any relief from several grains of morphine each day.

In all fifteen patients, relief from the itching was experienced immediately after the injection, and in only three was there marked swelling after the alcohol injection. In four cases no late follow-up was possible. In the other eleven the duration of relief varied. In one of the two patients with inflammatory cervical involvement the relief lasted but a few days and then the itching partially returned. It was severe

around the clitoris and at the fourchet, but practically absent around the labia. In the other patient with inflammatory cervical disease the relief lasted for one month. Both of these patients are under treatment for the endocervicitis. In another case relief was transitory. This patient subsequently was given electrocoagulation of the vulva for leucoplakic kraurosis. In one patient relief after the first injection lasted two months. Nine months have elapsed since the second injection, and there is still no recurrence of the itching. In one patient injected three times, the intervals of freedom from itching were three months, four months, and now three years. In another patient injected eight times, the intervals of freedom were two months, two months, four months, four months, two years, one year, two years, and now two years. Excluding the first three patients mentioned, in whom relief was obtained for only a few days to one month, the shortest period of relief was two months, the longest four years. The average period of relief was 13.6 months. If we include these three cases, the average period of relief was 11.7 months. In four patients the itching has not recurred to date. The interval in these patients is nine months, fourteen months, three years, and four years.

Alcohol injection for pruritus vulvae of unknown origin affords prompt relief from itching. Even though recurrence of symptoms may subsequently take place, the procedure is well worth while for the complete comfort it brings about in the free interval, and it can be repeated as often as necessary.

This method of treatment should be more extensively utilized, and be given preference to less effective or more drastic remedial measures.

I am indebted to Dr. Walter T. Dannreuther, Director of the Department of Gynecology, for permission to include his personal cases in this paper.

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151 WEST 77 STREET

## FULL-TERM PREGNANCY COMPLICATED BY RUPTURED SPLENIC ANEURYSM

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**A**NEURYSMS of the splenic artery are unusually rare. Since pathognomonic signs of splenic aneurysms are absent, the diagnosis is usually not made until rupture occurs. This is especially true, when it is associated with pregnancy.

A study of splenic aneurysms made by Schroeder<sup>1</sup> showed, that of 32,768 autopsies performed in Europe, only twenty cases of splenic aneurysms were included. It is of interest to note, however, that of the fifteen case reports reviewed by Lower and Farrell,<sup>2</sup> three cases were associated with pregnancy. One of these was reported by Saenger<sup>3</sup> in an eight months' pregnancy. The patient was suddenly seized with abdominal pain, followed shortly by collapse. On exploration, free blood was found in the peritoneal cavity, which led to the discovery of a ruptured splenic aneurysm.

The second case was described by Lundwall and Gödl,<sup>4</sup> in which a ruptured aneurysm occurred during the ninth month of pregnancy. Because of bleeding in the abdominal cavity, a supravaginal hysterectomy was done; however, the source of bleeding was not discovered until after the patient died. An autopsy revealed a ruptured aneurysm of the splenic artery.

The third case was reported by Smith,<sup>5</sup> which occurred in a negress, who entered the hospital in shock, with the diagnosis of a ruptured ectopic pregnancy. During laparotomy free blood was found in the lesser peritoneal cavity and further examination showed a ruptured splenic aneurysm. Although bleeding was controlled with tampons, the patient died two hours later.

The following case is presented, because of the rarity of this condition, and the difficulty in making a diagnosis, particularly when complicating a full-term pregnancy.

#### CASE REPORT

Mrs. R. O'G., a white multipara (para iii), thirty years of age, had been under our obstetric care for her two previous pregnancies, and was delivered uneventfully. She came under observation for her third pregnancy at the end of the second month of gestation. The first day of her last menstrual period was on June 22, 1933. She was seen at regular intervals for the balance of her pregnancy, during which time no abnormal findings were elicited. Her blood pressure varied from 100/60 to 128/82. At times a trace of albumin was noted in the urine. There was a systolic murmur at the apex, transmitted to the axilla.

The patient was last seen at the office on March 31, 1934. On April 1, 1934, at 3:30 A.M., she was suddenly awakened with severe pain in the epigastrium, accompanied by vomiting and pain in the right shoulder. She was advised to enter the hospital immediately. On admission at 6:35 A.M., she stated that she felt somewhat better, but still had pain in the upper left abdomen and right shoulder.

Examination at this time revealed the patient acutely ill, not in labor, but with a pinched face, cyanosis of lips, and shallow breathing. The temperature was 98.4° F., the pulse was 88 and regular. The blood pressure was 114/82. The uterus was enlarged to the size of a full-term pregnancy. The abdomen was slightly tender throughout, but more marked in the epigastrium, with moderate rigidity. The uterus was not contracting. The rectal examination showed no dilatation, cephalic presentation and a minus two station. The blood count showed 4,100,000 red cells, 18,300 white, 55 per cent hemoglobin (Sahli) with slight anisocytosis and poikilocytosis. The differential count showed: polymorphonuclear cells 90 per cent, small lymphocytes 6 per cent, large lymphocytes 3 per cent, and one transitional cell. The urine examination was negative.

A diagnosis of a ruptured viscus was suspected and she was kept under very careful observation. Repeated blood examinations showed no marked changes from the first examination. The pulse fluctuated from 72 to 96.

At 8:30 P.M., the patient attempted to leave the bed and she experienced again severe pain in the epigastrium and left shoulder blade. This was associated with dyspnea, cyanosis, nausea, and vomiting. The pulse became rapid and irregular. The fetal heart tones were 144 and regular. A diagnosis of intraabdominal bleeding was made. An injection of 1,000 c.c. of 5 per cent glucose in saline was started intravenously and an exploratory laparotomy performed. The peritoneal cavity was found to be full of blood. A low cervical cesarean section was done, and a live baby girl of seven and a half pounds was delivered. The abdomen was then explored for the source of bleeding.

Exploration revealed a large mass in the epigastrium, in the region of the lesser omental cavity. Meanwhile, the patient's condition became very grave. The pulse was about 170 and imperceptible at times. Because of her poor condition, the abdomen was closed rapidly. A blood transfusion of 570 c.c. of blood was given by the Scannell method. During the transfusion, a moderate improvement of the patient was noted, and the pulse became slow and regular. However, five minutes after the transfusion was completed, she again complained of severe pain in the

epigastrium and right shoulder. This was associated with a marked pallor, and the pulse became imperceptible. She died a few minutes later.

*Autopsy.*—The abdominal cavity was filled with free blood. There was a large clot in the lesser omental cavity. The hemorrhagic area extended into the retro-peritoneal spaces. The foramen of Winslow was open. The gallbladder was small and contained no stones. The uterus was contracted and extended just below the umbilicus. Both kidneys were of normal size. There was no rupture into the pedicle. The splenic artery as it transversed about the middle portion of the pancreas presented a ruptured dilatation about 15 mm. in diameter. The kidneys, liver, and spleen were pale. The adrenals showed no hemorrhages. The tubes and ovaries were enlarged, but showed no pathology.

*Anatomical Diagnosis.*—Ruptured aneurysm of the splenic artery at the bifurcation, prepancreatic hematoma, old and recent blood clots in greater peritoneal cavity, and acute anemia of all organs.

Microscopic examination showed the splenic artery slightly sclerosed in the media. The aneurysm was probably of a congenital origin.

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3460 LAWRENCE AVENUE

## ABRUPTIO PLACENTAE COMPLICATING TWIN PREGNANCY

L. A. BALASQUIDE, M.D., PONCE, PORTO RICA

(From the Obstetrical and Gynecological Service of the "Surgical Clinic of Dr. Pila)

**A**BRUPTIO placenta is always a serious condition. Its presence in twin pregnancy greatly endangers three lives. The maternal fatalities, according to available statistics, range from 2.6 to 66 per cent, while the fetal mortality varies from 60 to 95 per cent. The present case of abruptio placenta complicated a bioval twin pregnancy near term, with hemorrhage, treated by cesarean section, with recovery of the mother and one child.

L. M. G., white, school-teacher, aged twenty-six, primipara, near term, entered the hospital, March 10, 1934, because of vaginal spotting and pain in the right lower quadrant of the abdomen. She had been married for a year and four months, and had an abortion two and a half months after marriage. The past and family history was essentially negative. Menstrual history normal. The probable date of confinement was March 28, 1934. She received prenatal care elsewhere. She reached the ninth month of pregnancy without any evidence of toxemia or any other complication. There had been no edema or headache. She was admitted at 1:00 P.M. and was placed under close observation. At 4:00 A.M. next morning, I was hurriedly called because of profuse bleeding. She was very pale and complained of pain in the lower abdomen. The abdomen was greatly enlarged and its walls quite rigid. The uterus was also abnormally large, tense and rigid. There were no uterine con-

tractions. The fetal parts and heart tones could not be obtained. There was marked tenderness in the right lower quadrant and moderate vaginal bleeding. The vagina contained many clots. Rectal examination revealed the cervix hard, high and barely admitting the tip of the index finger. The head was not engaged. The blood pressure was 100/68, temperature 98° F., pulse 120, and respirations 30. Urinalysis was negative. Hb 60 per cent (Dare). Red blood cells 3,828,000. Coagulation time (Bogg) three minutes. Wassermann was negative. A diagnosis was made of abruptio placentae with severe internal and moderate external hemorrhage with intrauterine death of the fetus. One thousand cubic centimeters of 10 per cent glucose were given intravenously and  $\frac{1}{6}$  gr. of morphine by hypodermic injection. She was transferred to the operating room and a classical cesarean section performed. After incision of the uterus a twin pregnancy was revealed. The first placenta was completely separated from the uterine wall by large, dark clots and fluid blood. A stillborn female ( $3\frac{1}{2}$  pounds) was delivered. The second child, also a female, was living and weighed 6 pounds and 4 ounces. The placenta which was well attached was manually removed. It was normal in appearance, but smaller than usual. The detached placenta was very small. It weighed 8 ounces. It showed an acute brownish red infarct on the maternal surface. The consistency of the infarct was more homogeneous and slightly firmer than the surrounding normal placenta. Microscopically it revealed dilated, engorged, and occasionally ruptured capillaries and veins in the villi. There was also severe necrosis of the syncytium, Langhans layer and the stroma, and absence of the intervillous hyaline substance.

The patient had a rapid and uneventful recovery. She was discharged on the sixteenth day in fine condition. The baby gained in weight during the stay in the hospital.

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Cuizza, Tito: *Cardiopathy in Pregnancy*, *Monitore ostet.-ginec.* 6: 200, 1934.

Among 2,000 women delivered in the Institute of Obstetrics and Gynecology of Torino, 20 were cardiopathies. They fall into the following groups: (1) Patients at term or in last months of pregnancy, cardiac disease well compensated, slightly or badly decompensated. (2) Cardiopathic pregnancy in the first months of gestation.

Of 73 pregnancies in these 20 women 12 (16.7 per cent) ended in abortion, either spontaneously or artificially; 47 (64.3 per cent), reached term; and 14 (19 per cent) ended prematurely. Of the 47 babies born at term, 5 (10.6 per cent) died at birth or a few days later, and also 2 of the 14 premature babies.

In his opinion the maternal prognosis is good for the majority of the cardiopathic cases in pregnancy. The author places more importance on the functional capacity than anatomic lesion of the heart. In rare cases with grave decompensation early pregnancy is interrupted. In all other cases it should be attempted to carry pregnancy to full term. Labor in most cases is spontaneous.

The fetal prognosis is good for the newborn at term in well compensated cases. Prognosis is doubtful for premature infant or in instances of grave cardiopathy.

AUGUST F. DARO.



# Department of Maternal Welfare

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CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

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## COMPARABILITY OF MATERNAL MORTALITY RATES IN THE UNITED STATES AND CERTAIN FOREIGN COUNTRIES

ROBERT L. DE NORMANDIE, BOSTON, MASS.

THE claim has been made frequently that the maternal mortality rates in the United States should not be compared with those of other countries, that the methods of assignment of maternal deaths were so different that it was unfair to the United States to make this comparison, and that were comparability possible, the United States would not stand so high as it does in the list of nations. Therefore we welcome the study that has just been published by the Children's Bureau on the "Comparability of Maternal Mortality Rates in the United States and Certain Foreign Countries." This was initiated by a subcommittee of the Committee on Prenatal and Maternal Care of the White House Conference on Child Health and Protection. Dr. Tandy, Director of the Statistical Division of the Children's Bureau, was in charge of the investigation and wrote the report.

In order to obtain data that would throw light upon the effect of the differences in assignment procedure upon the comparability of maternal mortality rates, 1,073 United States death certificates on which pregnancy or childbirth was mentioned were chosen for study. These deaths occurred in 1927 and the certificates were chosen at random but represented every type of puerperal death. In this list there were many that were identical or very similar, and for transmittal to the foreign countries 477 certificates were carefully selected so as to include at least one death from every type in the sample. These 477 certificates were set up in a list form showing the primary and contributory cause of death, performance or nonperformance of operation or of an autopsy. Two blank spaces were provided, and it was asked of the foreign countries that the first of these columns be checked if the death could be classed as puerperal, and the second if it would be classed as nonpuerperal by the statistical bureau in charge of coding cause of death in each country. No information was given in these certificates in regard to the cause assigned in the United States.

These lists were sent to 24 foreign countries and answers were returned by the following 16: Australia, Canada, Chile, Czechoslovakia, Denmark, England and Wales, Esthonia, France, Irish Free State, Italy, Netherlands, New Zealand, Northern Ireland, Norway, Scotland, and Sweden. After these lists had been returned, the 596 deaths in the original group not sent abroad but identical with those that were sent, were classed as puerperal or nonpuerperal in accordance with the assignments made by the foreign countries for those that had been transmitted. The groups of deaths were then thrown together and a tabulation of the 1,073 certificates was prepared showing the assignment of the United States Bureau of the Census and the classification as puerperal or nonpuerperal by each of the foreign bureaus that complied with the request.

Some very interesting facts were obtained from this classification. The United States assigned to the puerperal state 92.9 per cent of the 1,073 deaths associated with pregnancy and childbirth. Denmark alone would have assigned more deaths than the United States. She would have classified 99.4 per cent as puerperal. Norway would have assigned the fewest, 76.9 per cent. England and Wales came next to Norway with 78.7 per cent. The United States assigned to the nonpuerperal causes 7.1 per cent, while Norway would have assigned 23.1 per cent and Denmark 0.6 per cent. Australia, the Netherlands, New Zealand, and Scotland made assignments in approximately the same ratio to puerperal and nonpuerperal causes as did the United States. This is as might be expected for the first three countries have officially adopted the United States *Manual of Joint Causes of Death* and Scotland also makes use of it although never officially adopted.

This study shows that although in some of the countries the methods of assignments to the various rubrics are similar there are real differences in procedure. In some of the countries infectious diseases resulting in high mortality are given preference to puerperal causes. In others this is not followed. The assignment of cardiac conditions varies, yet pulmonary tuberculosis is generally considered a primary cause. By most of the countries acute nephritis is regarded as another name for puerperal albuminuria and convulsions, but by some it is not so classified. There is no agreement among the countries in regard to embolism or to the large number of deaths due to abortions.

General rules for procedure are in use in the various statistical offices, but there are real differences which lead to slight alterations in the assignments, and therefore render statistics not completely comparable. Tables are given in the study showing the percentage change that would have obtained in the United States under the assignment procedure of the different countries which answered the questionnaire. The best position that the United States could have achieved would have been fifth from the highest, and under every system of assignment it is seen that the United States has a high maternal mortality rate. This study shows that we must admit our rate is high, and that within certain limitations comparability is possible. It brings out clearly, however, that our rate is falling—slowly, to be sure, but steadily—while in several of the countries the mortality rates are significantly higher, Canada alone showing a distinct drop.

Two factors: the first, differences in definitions of live births and the second, variations in the completeness of registration, are frequently mentioned when the comparability of the statistics of the United States and foreign countries is questioned. This study shows that complete unanimity in the definition of live births should prevail, and that it is essential to have complete birth registration, but even with differences which might arise from these two factors they are inadequate to explain more than a few points our maternal mortality, and we would still retain a high position in the maternal mortality rate list of nations.

In conclusion the following recommendations are made:

1. It would be desirable for the United States Bureau of the Census to publish annually a table showing deaths associated with pregnancy and childbirth by primary and contributory cause and also a table showing deaths associated with pregnancy and childbirth by states, by color, in urban and in rural districts in the states.

2. An investigation of the differences in assignment procedure and the formulation of rules uniformly acceptable to important countries should be undertaken by the International Statistical Institute at an early date.

Dr. Tandy's study is an important contribution to a more complete understanding of maternal mortality rates. It shows conclusively that the statistics of other

countries and ours cannot be compared with absolute fairness. Yet the variations are not so great that the statistics do not give investigators a clear and concise understanding of the conditions in the various countries. For years physicians and others interested in our maternal mortality rates have insisted that because of this lack of comparability, it was unfair to place the United States so high in the list. This report shows clearly, however, that even with the kindest consideration our position in the list of nations would not be materially altered.

The study is a further challenge to the medical profession to make added effort to improve the maternal mortality rate. The medical profession alone cannot accomplish this. The education of the women, and the men also, of the country must be insisted upon. Community responsibility for this condition is real, but the medical profession must be the leaders in the effort to lower the maternal mortality rate.

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Peckham, C. H.: *An Investigation of Some Effects of Pregnancy Noted Six Weeks and One Year After Delivery*, Bull. Johns Hopkins Hosp. 54: 186, 1934.

The stillborn and neonatal mortality rates were high, even for a clinic population with a large percentage of referred emergency cases. If women would apply early for prenatal care, and after delivery would attend regularly the child welfare clinics, the rates would be lowered appreciably. The black women were more successful in nursing their babies than the whites. The percentage of nursing mothers was high. Even if the supply of breast milk was insufficient ten to fourteen days after delivery, it often became adequate later. The incidence of perineal tears, relaxed vaginal outlets, cervical tears, and subinvolution of the uterus were greater in the white than in the black race. The ultimate result to the perineum in a series of cases not treated by routine episiotomy was good, only 1.31 per cent of the primiparas being left with marked relaxations. Probably as a result of too rapid resumption of household duties 10 per cent of the primiparas and 12 per cent of the multiparas had definite subinvolution six weeks after delivery. About a sixth of the total number of patients had retroflexed uteri a year after delivery. The earlier in the puerperium an attempt is made to correct this abnormality the greater are the chances for success. Only 8.37 per cent, including multiparas, were left with faulty abdominal support as evidenced by diastasis of the recti muscles.

In 71.45 per cent of the cases menstruation recurred before the cessation of lactation. A fourth of the white patients and a third of the blacks again became pregnant in the first year after delivery. In only 2.77 per cent of the primiparas and 7.15 per cent of the multiparas was it felt that the child-bearing had had a deleterious effect. This is a very low figure in consideration of the social and economic environment of this class of patients.

C. O. MALAND.

## Society Transactions

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### NEW YORK OBSTETRICAL SOCIETY

MEETING OF OCTOBER 9, 1934

The following papers were presented:

**The Operative Treatment of Sterility.** Dr. Francis W. Sovak. This paper is a part of the chapter on the operative treatment of sterility contributed to the *Textbook of Gynecology*, edited by Carl Henry Davis.

Discussed by Drs. I. Rubin, Wm. H. Cary and E. A. Bullard.

**Two Years' Experience With Theelin Treatment of Gonorrheal Vaginitis.** Dr. James R. Miller. (For original article see page 553.)

This paper was discussed by Dr. R. M. Lewis.

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### BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 5, 1934

The following papers and discussions were presented:

**When to Operate in Ruptured Ectopic Gestation.** Dr. W. C. Meagher. (For original article see page 541.)

Discussion by Drs. H. M. Mills, T. S. Welton, S. A. Wolfe, C. A. Gordon, S. B. Schenck, L. S. Schwartz, and J. A. Driscoll.

**The Management of Prolapse of the Uterus.** Dr. C. A. Gordon. (For original article see page 547.)

Discussion by Drs. Cameron Duncan and A. Koplowitz.

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Vogt-Möller, P.: Treatment of Sterility and Habitual Abortion with Wheat-Germ and Wheat-Germ Oil (Vitamin E), *Acta obst. et gynec. Scandinav.* 13: 219, 1934.

A report is presented by Vogt-Möller of 25 cases of barrenness in women, especially habitual abortion (20 cases) and sterility (5 cases), which were treated with wheat-germ oil or (and) with wheat-germ (vitamin E). The results obtained in habitual abortion are particularly favorable since the birth of a living child was attained in 17 out of 20 cases.

J. P. GREENHILL.

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Diseases of Respiratory and Circulatory Systems and Intestinal Tract Complicating Pregnancy

Maniscalco, S.: *Bronchial Asthma and Pregnancy*, *Monitore Ostet.-Ginec.* 4: 376, 1933.

The author presents a case of bronchial asthma which started at the second month of the fifth pregnancy of a woman thirty-six years old. History was absolutely negative to allergic conditions and respiratory infections. She had no history of childhood diseases except the typical winter colds. At the age of twenty-two, during a severe influenza epidemic, she had a bronchopneumonia with a high temperature for nine days. After ten years she was again stricken with a less severe bronchopneumonia. Three years later she had a third attack of moderately severe bronchopneumonia, recovery taking about three months. The patient never suffered with headaches, rhinitis, conjunctivitis, or urticaria.

She was in good health and entirely free from asthmatic symptoms while not pregnant. The patient suffered asthmatic attacks with each pregnancy.

Physical, including the obstetric examination was essentially negative except for the usual respiratory findings in asthmatics.

The remarkable feature of this case was the instantaneous disappearance of all symptoms following the artificial interruption of pregnancy. The author recommends interruption of pregnancy, provided the attacks are severe.

AUGUST F. DARO.

Turunen, A. O. I.: *Mediastinal and Subcutaneous Emphysema During Labor*, *Acta Obst. et Gynec. Scandinav.* 14: 76, 1934.

The author reports two cases in which young, healthy primiparas in connection with a normal, not unusually difficult delivery, were affected with subcutaneous emphysema in the upper part of the body and localized chiefly on the right side. In one of the cases the thoracic cavity was examined roentgenologically, and for the first time in a case of subcutaneous emphysema, air was shown to be present also in the mediastinum. Clinically it was proved that complete cardiac dullness had disappeared for several days. This testifies that, besides the subcutaneous emphysema appearing in connection with delivery, there is also present a mediastinal emphysema probably due to a subpleural pulmonary rupture. It is, therefore, presumable that the air in such cases wanders from the place of the pulmonary rupture into the mediastinum and from there finally under the skin.

As this complication is very rare and nothing seems necessary for evoking it except the usual great exertion at delivery, it must be presumed that its origin is promoted by congenital anomalies in the respiratory ducts or abnormal friability of the pulmonary tissues. Cases of mediastinal emphysema may occur in connection with delivery oftener than is believed, developing in exceptional cases to such an extent as to lead to subcutaneous emphysema.

J. P. GREENHILL.

Schroeder, C.: Physiology of Respiration During Pregnancy, *Klin. Wehnschr.* 12: 2067, 1933.

The author studied respiratory movements and pulmonary efficiency during pregnancy and the puerperium in a series of women by means of the pneumotachograph. He found that the respiratory mechanism remains normal throughout pregnancy with a constantly increasing respiratory rate and efficiency. This increase begins in the second month and continues until the end of pregnancy, and varies from 20 to 240 per cent. The return to normal is rapid during the puerperium.

RALPH A. REIS.

Rordorf, Roberto: Transplacental Passage of the Tubercle Bacillus Studied by the Löwenstein Method, *Arch. di ostet. e ginec.* 20: 627, 1933.

Study of 15 tuberculous women during labor, with active lesions, gave the following results: (1) The tubercle bacillus could not be found in the blood during labor by the cultural method of Löwenstein. (2) Blood from the cord of babies born of these same mothers also gave negative results. (3) The inoculation of guinea pigs with blood also gave only negative results. He concludes from his experiments that the tubercle bacillus does not pass through the placenta.

JAMES M. PIERCE.

Palanos Costa, N., and Falsia, M.: Transplacental Transmission of Tuberculosis, *Rev. Soc. argent. de biol.* 10: 207, 1934.

The authors obtained amniotic fluid from pregnant women frankly infected with pulmonary tuberculosis by abdominal puncture. The fluid was injected into guinea pigs. Out of 24 cases there was a positive guinea pig autopsy of tuberculosis in 12.5 per cent. Of 21 placentas obtained from pregnant women infected with pulmonary tuberculosis, 4.76 per cent gave positive guinea pig diagnosis of tuberculosis. It is concluded that it is possible to encounter an infected amniotic fluid with sound placenta, and vice versa.

MARIO A. CASTALLO.

Schultze-Rhonhof and Hansen: Critical Analysis of the Question "Tuberculosis and Pregnancy," *Med. Klin.* 29: 765, 1933.

The prevailing opinion is that active pulmonary tuberculosis is generally aggravated by pregnancy, a latent process is frequently activated and in such cases the pregnancy should be terminated early. However, this opinion is based upon scientific knowledge not as helpful as is available today. With proper medical attention pregnant women with tuberculosis may safely go through gestation. Even in Russia, where abortions are legal, and therefore there is no hesitancy about doing them, obstetricians have in recent years treated tuberculous pregnant women conservatively.

There is no doubt that pregnancy can aggravate the process but this is not the rule. The fate of a woman depends not upon the fact that she is pregnant but upon

the character of the lesion and upon the care she receives during pregnancy. Proper management of these patients lately has been considerably aided by lung surgery in the form of artificial pneumothorax, thoracoplasty, etc. These operations not only permit the continuation of the gestation but also have a favorable effect on the tuberculous process.

In the decision to perform a therapeutic abortion the social aspect must be considered. The problem of tuberculosis and pregnancy like the problem of tuberculosis in general is not only a medical but also a social problem.

The general outlook for babies born of tuberculous mothers is good. Thus in Blisnjanskaja's series of 23,000 children of tuberculous parents, raised in the country, only 7 became diseased. Intrauterine transplacental infection is extremely rare. The important thing is to avoid infection of the child after birth and this requires special care.

J. P. GREENHILL.

**Falkiner and Micks: Artificial Pneumothorax and Pregnancy, Irish J. Med. Sc., page 265, 1933.**

The authors record a case of successful pregnancy in a patient undergoing treatment by artificial pneumothorax for pulmonary tuberculosis.

Physicians see a relationship between pregnancy and phthisis in two ways. First, a previously dormant tuberculous lesion very often becomes active during the later months of pregnancy or very soon after a confinement. Such processes tend to be far more rapid in their evolution than in the nonpregnant patient. It is most important, therefore, that whenever pulmonary tuberculosis is suspected during pregnancy or after the puerperium an early diagnosis should be made with the object of instituting collapse therapy before the lesions have become extensively bilateral.

The second way in which the relationship obtrudes itself on the notice of the physician is by the problem of advising on the marriage of a patient actually under treatment for pulmonary tuberculosis. Should marriage and childbearing be postponed until after collapse therapy is over and done with (failing the eugenetically ideal course of forbidding marriage altogether)? A phthisical woman should not become pregnant, but if the patient rejects this advice, there may be advantages in allowing the pregnancy to occur while artificial pneumothorax is maintained, rather than waiting until reexpansion is permitted. There is a priori support for this contention, but the question cannot be decided without further evidence.

WM. C. HENSKE.

**Larrea, Ricardo: Laryngeal Tuberculosis and Pregnancy, Rev. españ. de obst. y gynec. 46: 479, 1933.**

From his study of laryngeal tuberculosis and pregnancy, Larrea concludes: (1) Tuberculosis does not cause sterility. (2) The prognosis is not always fatal since in cases with early lesions the process can be checked and later cured by adequate treatment. (3) The prognosis depends principally upon the general condition of the patient, but above all upon the form and evolution of the pulmonary lesions; the graver the pulmonary lesions, the less the probability of cure of the laryngeal involvement. (4) There should be sanatoria or special departments in hospitals for tuberculous pregnant women where they may be carefully observed during pregnancy. (5) The interruption of pregnancy should be the exception rather than the rule. (6) Labor should be terminated by forceps as soon as feasible to avoid the exertion of the expulsive stage.

JAMES M. PIERCE.

Seitz, L.: **Essential Pregnancy Hypertension as a Distinct Entity**, *Monatschr. f. Geburtsh. u. Gynäk.* 97: 325, 1934.

There occurs in some cases a distinct elevation of blood pressure during pregnancy and disappearance of this hypertension during the puerperium, without other apparent symptoms. This the author calls essential pregnancy hypertension. It is particularly noticeable at the end of gestation and during labor and is due to increased work to be performed by the circulatory system. The cause lies in a hormonal and neurologic basis, the diminution in cholin and increase in posterior pituitary hormone in the blood play a distinct rôle. Women who have goiter are particularly prone to develop this type of hypertension. The elevation in blood pressure may lead to disturbances in such parenchymatous organs as kidneys, liver, brain, etc. A hypertension which exists before pregnancy, as a rule, is aggravated by it. When the blood pressure rises above 250 mm. and decompensation disturbances arise, gestation must be interrupted.

J. P. GREENHILL.

Schroeder, Carl: **Work of the Heart in Pregnancy**, *Arch. f. Gynäk.* 150: 1, 1932.

The question of cardiac hypertrophy in pregnancy is still a moot one. The blood volume is but slightly increased while the speed of circulation is definitely decreased. The venous pressure remains practically unchanged. The general body metabolism is, however, markedly increased throughout pregnancy.

The author used the Grollman acetylene method for studying the cardiac output, heart minute-volume and investigated the arteriovenous differences in carbon dioxide tension by gas analyses. He finds a definite increase in the circulation during pregnancy due to an average increase of 27 per cent in the cardiac minute-volume. This latter increase is due to a definite and marked increase in cardiac rate in spite of a decrease in the cardiac output of each individual, cardiac contraction. This latter phenomenon is not due to a cardiac dilatation but is most probably caused by some degree of cardiac hypertrophy.

RALPH A. REIS.

Krukenberg, H.: **The Influence of Physical Labor on the Heart and Circulation During Pregnancy**, *Arch. f. Gynäk.* 149: 662, 1932.

The roentgen shadow of the heart in pregnancy becomes smaller following physical exertion. This decrease takes place in the longitudinal and transverse diameters as well as in heart volume. No cardiac enlargement was found in any of the patients studied in this series. The blood pressure of pregnant women rises rapidly following physical effort. It rises higher in pregnant than in nonpregnant women. The return to normal is much slower in the presence of pregnancy, especially in older women. The minute-volume of the heart is increased during pregnancy and here also the return to normal is slower in the presence of a pregnancy. When cardiac disease is present, the above changes become more marked.

RALPH A. REIS.

De Maria, Giorgio: **The Alkaline Reserve in the Pregnant Cardiopathic Woman**, *Clin. ostet.* 12: 645, 1933.

After repeated determination of the alkaline reserve in cardiopathic pregnant women before, during, and after labor, the author arrives at the following conclusions: (1) In the complicated cardiopathies the alkaline reserve is always diminished; the lower alkaline reserves are found in the grave cardiopathies with decompensation. (2) The lowering of the alkaline reserve is accentuated during



labor. (3) The alkaline reserve generally tends to return to its normal value in the puerperium. The promptness of alkaline reserve to return to normal is in direct proportion to the gravity of the cardiac condition. (4) Repeated alkaline reserve test in the pregnant cardiopathic before, during and after labor may be helpful in prognosis.

AUGUST F. DARO.

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## Item

### American Gynecological Society

The Sixtieth Annual Meeting of the American Gynecological Society will be held in Hot Springs, Virginia, May 27, 28, and 29, 1935.

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### American Board of Obstetrics and Gynecology

The general examination for all candidates for certification by this Board will be held in the Atlantic City General Hospital on Monday, June 10 and Tuesday, June 11, 1935, immediately prior to the scientific session of the American Medical Association.

Applications for Group A candidates must be received not later than May 1, 1935.

The annual informal dinner and general conference of Diplomates attending the American Medical Association convention will be held at the Traymore Hotel, Atlantic City, Wednesday, June 12 at 7 P.M. At this dinner the successful candidates from the examinations of the two preceding days will be presented in person, and short addresses will be made by several members of the Board.

For further information, booklets, and application blanks apply to the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, (6) Pennsylvania.

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## Errata

In Table II of Dr. L. A. Emge's paper, page 691 of the November, 1934, issue, the reference to von Graff, 1914, should read "sarcoma in rats" instead of "carcinoma in mice."

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In Table II of Dr. Torrance's article on page 437 of the March issue, the first subheading should read:

Comparison of Reaction in Rabbits Before, During, and After  
Pregnancy, With Virgin Animals

The heading for the second part of the table should read:

Unmated Controls

# American Journal of Obstetrics and Gynecology

VOL. 29

ST. LOUIS, MAY, 1935

NO. 5

## Original Communications

### CAN THE MORTALITY AND INCIDENCE OF CANCER OF THE UTERUS BE REDUCED?\*

JOHN A. MCGLINN, M.D., PHILADELPHIA, PA.

I SELECTED this subject because I desire the opportunity of recanting certain statements made in my inexperienced youthful years and to challenge certain accepted beliefs as to the cause of cancer of the cervix.

Twenty-five years ago, I arranged a cancer meeting in Philadelphia which was addressed by George E. Pfahler and Thomas S. Cullen and the late William L. Rodman. My contribution was a paper entitled "Cancer Mortality." I quote, "unless the public and medical profession are made to realize what a terrible scourge this dreadful disease is, we cannot hope to arouse sufficient interest and enthusiasm in the problem to render fruitful the truths which the subsequent speakers will enunciate." Then this gem of statistical research, "basing our results upon computations from the registration area for 1906, we find that between the ages of thirty-five and thirty-nine, one man out of forty-eight and one woman out of 13 will die of cancer; between forty and forty-four, one man out of 28 and one woman out of 8; between forty-five and forty-nine, one man out of 20 and one woman out of 6; between fifty and fifty-four, one man out of 14 and one woman out of 5; between fifty-five and fifty-nine, one man out of 12 and one woman out of 6; between sixty and sixty-four, one man out of 12 and one woman out of 7; between sixty-five and sixty-nine, one man out of 12 and one woman out of 8." These figures have been quoted freely in

\*Read by invitation at a meeting of the Brooklyn Gynecological Society, May 4, 1934.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

papers and textbooks during the past twenty-five years. I quote them again to correct a false statement and to show into what errors ill-considered statistical deductions may lead us.

In the registration area for 1906, there were 4,767,304 women over thirty-five years of age and of these 156,465 died from all causes, among which were 16,879 cases of cancer. My original paper stated that one woman in 9.2 per cent over thirty-five years of age will die of cancer whereas the truth is that one woman in 283 died of cancer and about one in 1,000 died of uterine cancer. These statements which have gone unchallenged for twenty-five years are on a par with many other beliefs which are just as ridiculous and unfounded.

Another paper entitled "The Relation of Gallstones to Cancer of the Bile Tract" was published in 1911. There were reported eleven cases of primary cancer of the gallbladder and five of the bile ducts. Gallstones were present in eight of the gallbladder cases and in three of the duct cases. A total of 507 gallstone cases were studied. From this paper I quote, "if we accept the theory of irritation as a cause of cancer, we can learn an important lesson in the treatment of the disease. I firmly believe that all the time and energy spent in inculcating the lessons of the necessity of early diagnosis are well-nigh wasted. The time to cure cancer is before it develops; in other words, we should teach how to prevent cancer. If gallstones are the cause of cancer of the biliary passages, then, if the stones were removed early, cancer would not develop. As to cancer of the biliary passages, I believe this principle of prevention should be applied to other organs of the body. If it is true that 75 per cent of gastric carcinomas are preceded by gastric ulcer, then every gastric ulcer operated on should be treated by the removal of the ulcer-bearing area (Rodman's teaching) and the operation of gastroenterostomy for this condition discarded. In cancer of the cervix uteri, we know that the great majority of the cases are preceded by a laceration of the cervix. While we might repair or amputate many a cervix where, in the light of future events, the operation might be considered to have been unnecessary, cancer of the cervix would be a rare condition if every woman nearing the menopause had a good cervix with no pathologic changes to produce irritation." Many other papers followed including one read at the Annual Meeting of the Medical Society of the State of New York, April 29, 1915, all decrying the hopelessness of attaining early diagnoses and stressing the theory of irritation as the cause of cancer and urging the eradication of precancerous lesions as a prophylactic.

Except that gallstones happened to be present in eleven out of the sixteen cases of cancer of the bile tract reported, there was not one whit of tangible evidence to prove that they were the cause of the cancer and all my deductions were fanciful at least.

Arguing from another standpoint, it would have been a more justi-

fiable though a ridiculous deduction, that inasmuch as only eleven out of 507 gallstone cases developed cancer, gallstones prevented cancer. It might also be pertinent to ask what caused the cancer in the 5 of the 16 patients who did not have stones. It is on just such flimsy evidence that many of our beliefs as to the cause of cancer are based. Picture what would have been the end-results if the 507 had their gallbladders removed to prevent the occurrence of the eleven cases of cancer.

You will note in the quotations just read that the profession was awake twenty-five years ago in a fight to cut down the incidence of cancer of the cervix by eradicating the supposed precancerous lesions. During that period untold thousands of cervixes have been repaired, amputated, coned, cauterized, electrolized, etc. Is it not about time to take an account of stock and see what has been accomplished by this long and intensive campaign? I am now about to make a statement which will shock many of you; I am convinced that lacerations and chronic irritative lesions of the cervix play but little part in the causation of cancer, and our efforts for the past twenty-five years in clearing up these lesions have not reduced the incidence of the disease.

In the first place, we have been grossly exaggerating the frequency of cancer of the uterus. In 1900, the population of the United States for females over thirty-five years of age was approximately 9,000,000 and of these about 8,500 died of cancer of the uterus. Allowing a cure rate of 25 per cent, the total number of cases was approximately 10,625 or one case in 900 women of that age period. From 1900 to 1932, the population of the continental United States has greatly increased and particularly in the age periods constituting the cancer years. The increase in this particular period of life has been brought about by the prolongation of life in middle age and lessening of the population in the early periods by the rapidly falling birth rate due to birth control propaganda. It is natural then to expect to find a greater number of cases now than in 1900. In 1932 for continental United States exclusive of Utah, only 14,871 deaths from cancer of the uterus were reported. In one of the most recent papers on this subject, Crossen reports that for a five-year period, 1921 to 1926, 121 patients were treated in the Barnes Hospital or an average of less than 25 patients a year, surely not an alarming number of cases. In my clinic at the Philadelphia General Hospital, we examine about 200 women every Saturday. So far this year we have not had a case and last year we had but one case. I am citing these figures, not to minimize the importance of this subject but to counteract, for the sake of truth, the unfounded statements that I and others have been guilty of making as to the incidence of cancer of the cervix.

In Crossen's paper, we find this statement which well expresses the view generally held now and for many years past. "It is well estab-

lished that cancer of the cervix comes from long continued irritation in the form of chronic cervicitis, usually accompanied with lacerations, eversion, infiltration and cystic changes."

On what foundations is this belief built? First and foremost on the theory that continued irritation and traumatism of tissue is the cause of cancer. Natives of Kashmir wear hot charcoal stoves next to the abdomen and develop cancer of the abdominal wall. Clay pipe smokers develop cancer of the lip; workers in pitch and aniline dyes develop cancer of the skin. Gastric cancer is preceded by gastric ulcer in 75 per cent of the cases. Sarcoma of bone and other tissues often follow a single injury and cancer of the breast follows trauma. Cancer of the cervix is more frequent in married women and in those who have borne children than in the unmarried. This list can be extended almost indefinitely. Tissue growth (malignant) can be stimulated experimentally by mechanical and chemical irritation. Studies have been made showing the incidence of cancer less in those women where the irritative lesions of the cervix were adequately treated than in women in which the cervix was either inadequately treated or not treated at all.

As the cause of cancer is not known and as authenticated cases of cancer have apparently followed traumatism, no one would be justified in stating that traumatism and irritation play no part in the causation of cancer. On the other hand, I believe that one is justified in stating that trauma and irritation in themselves do not cause cancer and that cancer might and probably would have developed in the individual even if the factors of trauma and irritation had not occurred.

Are not the pipe smokers, the pitch and aniline dye workers, the bone sarcoma and the cervical cancer cases in the same category as my 507 gallstone cases? For every clay pipe smoker who develops cancer there are hundreds of smokers who do not develop the disease, and hundreds of people develop cancer of the lip who never smoked at all, or had any other irritation of the lip. Gastroenterologists no longer believe that gastric cancer is preceded by gastric ulcer in 75 per cent of the cases. Many of them now hold that cancer of the stomach starts as cancer and that ulcer plays little if any rôle in its causation. Even if we accept the view that gastric cancer is preceded by ulcer, we must admit, frequent as it is, that cancer cases are relatively few as compared to the ulcer cases. Today there are at least 12,000,000 women over the age of thirty-five living in the United States of whom probably 10,000,000 are or have been married. It would be a conservative estimate that 9,000,000 have had children and that 8,000,000 have cervical lacerations, eversions, erosions, cystic degeneration, or chronic endocervicitis. Of these only 14,000 develop cancer in any one year. Of course, 14,000 or more will develop cancer the next year

but other thousands who will not develop cancer are coming up every year from the lower age brackets. In other words, for every woman over thirty-five years of age who develops cancer of the uterus in any one year, there are between 900 and 1,000 women of the same age group who do not develop cancer of the uterus.

In a recent paper, Dr. Charles C. Norris quotes Saltzstein and Topcik to "show that of 18,562 patients who were treated by surgery or diathermy for cervical lesions, only 15 subsequently developed cancer." The same authors quote statistics which show that of 2,255 patients with carcinoma of the cervix, only 33 had received adequate treatment for chronic cervical lesions. The first series of cases does not prove conclusively the value of cancer prophylaxis. As cancer of the uterus (cervix and corpus) only occurs in 1 of 1,000 women over thirty-five years of age, we would expect an incidence of 18.5 per cent in the number of cases quoted. Fifteen cases actually developed cancer which shows, statistically, that only 3.5 cases were prevented out of a total of 18,562 cases adequately treated.

Having shown, statistically, that the cases published by Saltzstein and Topcik do not prove the value of cervical repair, etc., in preventing cancer of the cervix let us examine their original table and see what value it has, if any.

INCIDENCE OF CANCER FOLLOWING ADEQUATE TREATMENT OF CERVICAL LESIONS  
(From Saltzstein and Topcik)

Of 5,962 patients having had trachelorrhaphy, cervical amputation or cautery (Pemberton, 12)	5 developed cancer later
Of 3,650 patients having had cervical repair (Smith et al., 13)	6 developed cancer later
Of 1,150 patients having had cervical cautery (Smith, 13)	0 developed cancer later
Of 2,985 patients having had cautery or diathermy (Bland, 16)	0 developed cancer later
Of 4,815 patients having had cervical repair (Graves, 14)	4 developed cancer later
Of 18,562 patients having had adequate treatment	15 developed cancer later

The cases reported by Pemberton, Smith et al, Smith and Graves were all the same cases. Instead of 15,577 cases studied there were actually only 5,962 cases. Of the 4,815 cases reported by Graves only about 30 per cent were followed. Woolston was able to follow up over 1,000 cases of cervical repair who were operated upon more than ten years ago out of these same cases. There was an incidence of cancer of the cervix of almost 2 per cent of these cases or double the normal incidence of cervical cancer. The 2,985 cases credited to Bland were copied from a paper read March 26, 1930, before the Suffolk District Medical Society. As to these cases, Bland's statement is "the figures cited by Ralph R. Huggins are equally as dramatic. He reports 2,985 cases of chronic cervical disease treated by cauterization or excision by the endothermic knife without a simple case of cancer developing thereafter." Surely, an unverified quotation of a quotation of a quotation is

without value. Huggins states in a paper (read before the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, September 10 to 12, 1928), "We now use the cautery or excise the entire diseased area with the endothermic knife. We have treated 2,985 chronic cases by this method during the past ten years and seldom fail to cure the leucorrhea. During this time we have never found a case of carcinoma develop in the cervix of patients so treated. This number is too small, of course, for one to draw any conclusions as to the prophylactic results so far as malignant change is concerned." Yet in spite of this very fair and definite statement by the author, these cases were included in the table without the authors even consulting the original paper. The entire table is without value except to show on what ill-considered data our opinions are often based. To recapitulate: of the total of 18,562 cases reported, only 1,000 were adequately studied over a ten-year period and in these, the incidence of cancer of the cervix was double the normal incidence.

It has been stated that cancer of the cervix is more frequent in women who have borne children and married women than in virgins. It has also been stated that when it occurs in virgins, those affected have had a preexisting cervical irritation. The first statement is beyond question but as far as I know, the proportion of childbearing women to virgins who develop cancer of the cervix has never been adequately determined. The reports of death from cancer in married and single women do not answer the question. These reports only show the number of married women and the number of single women who die of the disease; they do not show the number of married women and the number of single women living in the community. To be of any real value, a five-year study should be made in a group of populous states. Such a study should show the total number of married women living in the area and the number who develop cancer of the cervix each year and the incidence rate calculated for this group, and it should show the same calculations for the unmarried group and the rates for the two groups compared.

As to the second statement: is this statement based on actual evidence or presumptive evidence? It has been my lot to see a great many virgins in the cancer years; women who never even had a douche or a vaginal examination. In this group, I have seen a number of cancers of the cervix and the only evidence of a preexisting cervical irritation was a vaginal discharge. A vaginal discharge does not always mean a lesion of the cervix. Vaginal discharges are common in this group. Examination at times reveals a simple erosion of the cervix and more often the cervix is entirely normal. Unless the actual condition of the cervix was known prior to the development of the cancer and the case followed, presumptive conclusions are of no value.

It is true that cancer can be produced in rats by repeated irritation with pitch or tar. While rats are prone to develop cancer, it is only in a comparatively small number of the experimental animals that the disease can be induced.

The most important question from the scientific standpoint is not to prove that irritation causes cancer but if it does, why it does in a limited number of cases and does not in an infinitely greater number? This statement has a practical application which will be discussed later.

In the discussion of prevention of cancer of the cervix and other parts of the body, many pathologists and clinicians speak of the pre-cancerous stage or lesion. What is this precancerous lesion? To the best of my knowledge, no one has ever definitely described such a lesion or proved its existence. As a matter of fact, pathologists cannot definitely diagnose cancer unless it is definitely cancer. All of us have removed uteri on the biopsy diagnosis of early cancer only to find after the minutest search no evidence of cancer in the gross specimen, and when the original studies are submitted to other pathologists, find them in disagreement.

For a number of years, we have been closely investigating, in our own services, this phase of the question. We, of course, see many cases of irritative lesions of the cervix, many treated inadequately and many not treated at all. I have never yet been able to follow any of these patients and see them develop cancer. Have any of you? Surely, if these lesions were the cause of cancer of the cervix, it should be a common rather than an uncommon experience. Again, both Schiller and Graves have pointed out that when the Schiller test is positive for malignancy, the lesion is found not in the irritated area but in the healthy tissue adjacent to the lesion.

Another important question to solve in this cancer problem is, why does the disease manifest such a selective action for the stomach, liver, female breast, and cervix uteri. In other than these organs, the incidence of cancer is minimal. If irritation plays such an important part in the cause of cancer, why are the lungs, the most frequently and most severely irritated organs in the body, so rarely the primary site of the disease. I am convinced that cancer is a primary disease, that it starts as cancer without any intervening change; if irritation plays a part, that it does so by breaking down tissue resistance and allows the disease to gain an impetus and to spread.

Now as to some practical considerations as to the possibility of reducing the incidence of cancer of the cervix. In the early part of my paper, I stated that the prevention of this disease by clearing up lesions of the cervix has been taught and vigorously practiced for the past twenty-five years. During this period, untold thousands of women have been treated, some to remain cured of irritative lesions and, of course, many to relapse. The proof of any method of cure can only be measured by the results obtained. Eliminating and balancing certain errors in statistical compilations, we would expect to find, if the method was of value, a reduction of the incidence of the disease. How-



ever, we find just the opposite; instead of a decrease we find an increase in the incidence of cancer of the uterus and the increase is progressing yearly. The latest figures from the Bureau of the Census show the following for cancer of the uterus: 1930, 14,074 deaths; 1931, 14,443 deaths; 1932, 14,871 deaths. The rates per 100,000 population for the corresponding years were 1930, 11.9; 1931, 12.1; 1932, 12.4. Pennsylvania has been most active for many years in cancer work. The State Society has an active and energetic Cancer Committee, and there is such a committee in practically every County Society. A special Cancer Week is held each year during which an intensive course for physicians is given in cancer prophylaxis, diagnoses, and treatment. A Speakers Bureau is maintained and lecturers are sent to speak to lay audiences at various times during the year. Addresses are made over the radio and a Publicity Bureau cooperates with the press in disseminating proper knowledge of cancer to the laity. This effort has gone on vigorously and unceasingly for years and yet our cancer rate has increased 25 points per 100,000 population during the past fourteen years.

If there is any one place where cancer prophylaxis has been well taught and carried out, it is New York and yet, the cancer death rate increased 27 points since 1920.

What is true of New York and Pennsylvania is true of the United States as a whole, the increase rate being 19 points for the same period. The idea of cancer prevention by removing the precancerous lesion is not new. The slogan "the time to cure cancer is before it develops" has been the heavy artillery and machine gun fire in the war against cancer for the past twenty-five years. Some notable victories have been won; cases are seen earlier and more cancers are being cured than ever before. Also as a result of better diagnoses and a clearer understanding of the disease, fewer people are being mutilated and killed in a vain attempt to remove what were supposed to be precancerous lesions. I refer particularly to operations on the stomach and female breast.

It has not been for the lack of honest and well-sustained effort on the part of the medical profession and cooperating agencies that control of cancer has resulted in failure. The trouble has been and is that our present knowledge of the disease is not sufficient to enable us to wield the armament both offensive and defensive to win the battle.

If we have lost our objective in the past twenty-five years, how can we hope to achieve it by the same tactics in the future? Even if it were true that every cancer of the cervix was due to irritative lesions, the campaign would fail. When we consider the widespread distribution of the millions of women with irritative lesions of the cervix, we might just as well try to save a sinking ship by bailing it out with a teacup.

Even if clearing up the cervix would prevent cancer, the number of women reached who could be kept permanently cured would be so small that the incidence would not be affected.

In order to prevent the occurrence of one case of cancer of the cervix in a year it would be necessary to maintain in a healthy state the cervixes of between 900 and 1,000 women during the same period of time—a totally preposterous and impossible proposition.

In a recent letter, Sir Herbert Spencer, strongly advises complete hysterectomy in fibroids as a prevention against cancer developing in the cervical stump. It is a laudable suggestion; it might save the occasional case. In its final results, it is comparable to my suggestion to remove the 507 gallbladders to save the eleven cases of cancer. In a recent study it was shown that the incidence of cancer of the cervix after subtotal hysterectomy varied from 0.0 to 0.4. It was also shown that cancer of the cervix develops as frequently in the stump of inflammatory cases as it does in the fibroid cases. An average incidence is 0.2, or once in 500 cases. I am sure it will be agreed that if complete hysterectomy was done in 500 consecutive cases of inflammatory and fibroid disease, that the resultant increase in mortality from the operation would greatly exceed the incidence of cancer developing in the stump.

I have voiced these views in several discussions in Philadelphia and grave heads have shaken and I have been labeled a dangerous teacher. In the few times I have presented my views on this subject my objective has been misunderstood. I am not favoring the abrogation of methods to restore or remove a diseased cervix. I do and will continue to do complete hysterectomies in uterine fibroids and other pelvic diseases to save the occasional case from a subsequent cancer of the stump, providing the increased risk to life from the operation is no greater than the incidence of the possibility of cancer.\* I also do now and advocated twenty years ago, a high amputation of the cervix in a grossly diseased cervix in women after the childbearing period. I also do an amputation of the cervix in all interposition operations and frequently resort to the Mayo operation in preference to the Watkins procedure. I also favor cervical amputation in the Fothergill or Halban operations in women past the childbearing period. I believe that, if the cervix or uterus is removed completely, the operation is a real prophylactic one, but I am not foolish enough to believe that even if such methods were generally adopted, that we would make any appreciable headway in the control of cancer.

Further, it is not my purpose to discourage operations or treatments on the cervix. There are many sufficient reasons why a cervix should be restored to normal or removed, other than cancer prophylaxis.

\*One of the three cases of malignancy which I have seen after hysterectomy was in the scar on the vaginal vault after a complete hysterectomy.

Neither do I advocate the public dissemination of these views. The belief that "tears" may lead to cancer has been accepted and is generally known by women. This fear brings women in increasing numbers each year to their physicians for observation and advice and thereby promotes the possibility of earlier diagnoses.

My object in presenting the opinions expressed in this paper are two: first, after an experience of many years, the theory that cancer of the cervix is caused by irritative lesions has not been proved so far as practical results have been attained in the reduction of cancer incidence by their removal. The adherence to a belief not sustained by scientific proof or clinical experience is not justified, as it is likely to detract from efforts along new lines to solve the enigma. Second, inasmuch as the irritative theory of cancer has not been proved, and that cancer does develop in diseased cervixes adequately treated and, in as far as we know, normal cervixes, it is not safe to assume that cancer will not develop in such cervixes. In six patients with cancer of the uterus recently reported in Philadelphia, two had had cervical amputations and one radium. To give a woman a false sense of security and to discharge her from further observations, after her cervix has been treated, with the statement that she is now safe from cancer is not justified. It is a bad state of mind for the physician to hold such views.

We have held these views too long and accomplished little or nothing in the fight against cancer incidence. What we must realize is that, after all, only a certain relatively small number of women will develop cancer of the uterus and that those who do are probably doomed to it whether they have cervical lesions or not. Our task is to develop some method, clinical or biologic, that will enable us to recognize this potential cancer group and apply radical measures, high amputations or vaginal hysterectomy before the cancer develops. We should make every effort to accomplish this end instead of spending all our thought and energy on the fruitless program we have been following for the past quarter century.

My title asks "Can the Mortality in Cancer of the Uterus Be Reduced?" Theoretically, it would be possible to cure 100 per cent of cervical cancer with our present methods, providing the treatment was instituted early enough. Practical experience has shown that curability depends on the early recognition of the disease and its prompt and thorough eradication. In order to obtain cases in the early stage, we must not only be able to get them in for examination but we must also be able to recognize the disease in its early stages. The campaign for periodic examinations must continue. While it was a mistake to consider the campaign for early diagnosis a failure, no great harm resulted as the effort to prevent cancer did bring many

women under observation. The campaign was not successful, not that an increasing number of women failed to report for examination but because we failed to recognize the earliest signs of the disease. It is frequently stated that cancer of the cervix is a symptomless disease until it is far advanced and hemorrhage and discharge result. For many years we have been sold on the idea that these two are the cardinal symptoms. So fixed has been this idea that we have failed to study the possibility of other symptoms preceding these classic ones. When we note the extent of the lesion after the first bleeding brought the patient for examination, it is hard to conceive of a lesion of such extent and character not producing symptoms. Extensive clinical observation is necessary to discover, if possible, some early characteristic symptom complex: it may be of a local or general character.

In the routine examination of cases, we must develop new methods for the early diagnosis of cancer, as our present methods are inadequate. Biopsy studies are of little value except in cases which are definitely cancer and which, in the majority of cases, can be diagnosed clinically. There are too many positive and negative errors in the early cases. The difficulty is that there is not a definite histologic picture that will determine a precancerous lesion or a transitional stage, if such lesions exist. If the biopsy is definitely positive or definitely negative, histologic studies are of real value.

Lately, much work has been done on early diagnosis by differential stain and by illumination plus magnification. I have not had sufficient experience with either the Schiller test or the colposcope to evaluate them. Every effort should be expended to develop these and other methods so that very early diagnoses can be made.

In conclusion I would state that with our present knowledge of cancer, we have no reason to hope for a reduction of the incidence of the disease. On the other hand, we can hope for a great reduction of mortality by educational methods to induce women to submit to periodic examinations and the development of methods to make earlier diagnoses possible.

1900 RITTENHOUSE SQUARE

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**Basden, Margaret M.:** Volvulus of the Cecum Complicating Labor, *Brit. M. J.* 1: 1119, 1934.

An interesting case of volvulus of the cecum complicating labor in a twenty-three-year-old primipara is described. The patient was considered to be in labor for the first forty-two hours after admission before the complication was suspected. The outstanding symptoms were dyspnea and vomiting. Four hours later an exploratory laparotomy was performed and a twisted, dilated cecum relieved.

The author advises laparotomy even during labor or early puerperium whenever an intraabdominal disease is suspected.

F. L. ADAIR AND S. J. BENENSOHN.

## A PREDISPOSING FACTOR FOR THE NORMAL ONSET OF LABOR: THE PROBABLE RÔLE OF ESTRIN\*

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AT THE outset, one can hardly do better than to quote from a dissertation "On the Contractions of the Uterus," written in 1847 by William Frederick Barlow. "There can scarcely be," he begins, "a more interesting and important inquiry to the physiologist than the nature of uterine contractions, and certainly it requires further investigation."

Since that time Barlow's injunction has been well followed as may be judged from the recent reviews by Gibbons,<sup>1</sup> Allen and Dodds,<sup>2</sup> and Robson.<sup>3</sup> The result of this multiplicity of work has been a host of theories particularly as regards the causative factors for the onset of labor.

One of the recent theories, first suggested by Dr. Jeffcoate,<sup>4</sup> of Liverpool, appears to merit special consideration. It embodies a view which has been growing with increasing conviction in the minds of a number of investigators whose opinion has been guided by a variety of experimental evidence from several different laboratories.

Briefly stated this theory may be worded somewhat as follows: Inasmuch as one substance (or class of substances), estrin (theelin), is essential for coordination of all in vivo uterine contractions and inasmuch as in its absence coordinated uterine contractions have not been demonstrated to exist, it may be postulated that the presence of estrin is a necessary condition for labor. It should be emphasized that this theory is not meant to imply that estrin acts alone. Rather, it merely states that *estrin is indispensable to the act of parturition*.

The present basis of the theory of the primacy of estrin for the onset of labor receives support from at least three lines of evidence. The first of these is the specific motility-inducing property of estrin upon uterine muscle as undeniably established in animals; the second, the evidence that estrin exerts a similar effect on the human uterus; and third, the evidence that during gestation in the human being, estrin is present in increasing amounts, reaching its highest level at the time of the onset of labor. These conditions may be associated to form a factor initiating a coordinating mechanism of labor, such as will shortly be described.

\*Read before the Brooklyn Gynecological Society, November 2, 1934.

*Effect of Estrin on Uterine Muscle in Animals.*—For about twelve years very good data from excised uteri have indicated that marked uterine contractions occur at the time of estrus in the rat, mouse, sow, cow, guinea pig, and other animals, whereas in anestrus, diestrus, pregnancy, or pseudopregnancy, the uterus shows little or no motility. When attempts were made, however, to show a causal relationship between the estrus-inducing hormone, estrin, and the marked uterine contractions of estrus, less satisfactory data were forthcoming. Some investigators found no effect at all of estrin on spontaneous uterine contractions. Others adduced evidence to show that it even depressed such motility as existed, while a few obtained uncertain evidence of an augmentation of motility of the excised uterus when estrin is added to the bath (Hisaw,<sup>5</sup> Reynolds,<sup>6</sup> Robson<sup>3</sup>).

The first undeniable evidence which shows the direct action of estrogenic substances on the uterus is found in the work of Robert T. Frank and his associates in 1925.<sup>7</sup> These investigators observed that if a castrated rat is injected with estrin and the motility of the excised uterus tested twenty-four hours later, such uteri regularly show rhythmic contractions of considerable force and amplitude. This fact has received confirmation on a number of recent occasions.

Soon after this report I undertook studies at the suggestion of Dr. M. H. Friedman which led ultimately to the development of a method of recording uterine contractions in chronic experiments on unanesthetized rabbits. The advantages of such a method over the surviving uterus technic are obvious. The uterus receives its own blood supply, the innervation is intact, and the temperature of the uterus is normal. Most important of the advantages, however, from the standpoint of an investigator, is the fact that the method lends itself to controlled experiments with the same uterus from day to day for extended periods of time. The uterine fistula technic in both principle and practice is not difficult to perform.<sup>8, 9, 10</sup>

By virtue of the controlled nature of the experiments thus far carried out, it is now possible to make the definite statement that estrogenic substances are the only ones that are capable of inducing rhythmic contractions in the quiescent uterus of, for instance, a castrated rabbit. In the absence of estrin, uterine quiescence supervenes. This is exemplified in the following conditions. At estrus (when a rabbit will receive the male and ovulate in response to the stimulus of coitus) rhythmical contractions are found, whereas they do not occur when the rabbit is not in heat. Now, if a rabbit whose uterus is contracting rhythmically is deprived of her ovaries, motility invariably subsides within several days, and the administration of a small amount of estrin readily brings about a restitution of motility of the precastration type within twenty-four hours. The replacement effect of estrin

is specific, moreover, for no other drug or hormone preparation has been found which is able to simulate estrin in its effect on motility of the uterus. In this respect, the hormone estrin stands alone.<sup>11</sup>

Since these facts were first reported, they have received independent confirmation in in vivo experiments by Professor Blair-Bell and his associates<sup>12</sup> of Liverpool, as well as by Morgan of Professor Clarks' laboratory in Aberdeen.<sup>13</sup> Also the method has been used satisfactorily by Friedman and others in several laboratories in this country.

Most important for the present consideration is the recent work of Pompen, from Professor Laqueur's laboratory in Amsterdam.<sup>14</sup> This work not only confirms the fistula observations, but extends them as well. In careful experiments with an abdominal window, Dr. Pompen calls attention to the fact that the estrin-induced rhythmic uterine contractions in reality represent activity in which contraction waves start at the tubal end of the cornua and sweep downward to the vagina. As the effect of estrin wears off, the contraction waves tend to become less and less coordinated as well as less powerful, with the result that they die out before progressing very far. Eventually, only feeble, uncoordinated contractions may be seen over the whole surface of the uterus.

The point, then, to which I particularly direct your attention is this: not only is estrin indispensable for powerful contractions of the uterus in vivo, but also its effect is mediated at least in part by a coordination of otherwise feeble, ineffective contractions. We now come to the second point of our consideration.

*Evidence in the Human Being of the Action of Estrin on Uterine Musculature.*—What is the evidence from human being in vivo observations that uterine motility is indispensably associated with the presence of estrin? Admittedly, evidence from this source necessarily must be meager, for the nature of the subject does not permit of fully controlled experiments such as may be performed on lower animals. The investigator must be guided, therefore, by inference and compare the few observations which daringly have been made from time to time on human subjects with the more fully controlled conditions of parallel states in in vivo experiments performed thus far only on the rabbit.

Although records of uterine contractions have been obtained from human subjects since 1872 when Schatz introduced a bag into the parturient uterus, the advances in our knowledge have been concerned chiefly with the effect of drugs in order to discern their action on the human uterus directly. While of much use pharmacologically and therapeutically, these methods have recorded motility at a time of stress when the devices of experimental procedure are reduced to a minimum. Several recent studies have yielded data of some physio-

logic interest, however. Moir of London, Dodek, and Barlow, from Cleveland, have recorded uterine contractions during the first two weeks of the puerperium, at a time when the ovary is in the follicular phase of the sex cycle. At this time one finds rhythmic contractions of considerable amplitude, which, except for differences in time relations, resemble the coordinated contractions seen in the uterus of the rabbit. From a physiologic point of view, of course, the puerperium may not be an optimum time for such studies.

Probably more typical, and certainly more complete, data have been forthcoming from the ingenious method devised and extensively used by Professor Knaus of Graz.<sup>15</sup> Iodized oil is introduced into the cavity of the uterus and a tube connected with a recording system is inserted through the cervical canal and brought into free communication with the oil distended cavity. Knaus has found that only during the period of menstrual flow and up to the midinterval of the cycle does the uterus react to the injection of pituitrin, while in the latter half of the cycle, concurrent with the formation and functioning of the corpus luteum, no pituitrin response can be elicited. With minor variations, these observations have been confirmed by Wittenbeck. In view of the current opinions that seem to have the weight of evidence in their favor, one may say that the period of ovarian follicular activity coincides with the period of highest uterine reactivity to pituitrin. This agrees with the more extensive *in vivo* observations on the rabbit by Pompen, Blair-Bell and myself, all done independently.

Schultze<sup>16</sup> in similar experiments found by means of roentgenographs that the uterus is so irritable in the early interval, and up to the midinterval, that it does not retain the lipiodol, but passes it up the tubes. He finds this is not so in the late cycle for the uterus retains the oil and as a consequence becomes distended. Although Schultze interprets his observations differently from Knaus, the latter investigator points out by means of sound physiologic reasoning that only the interpretations, and not the facts which Schultze records are inconsonant with the view that during the follicular phase of ovarian activity, the uterus is more active and more irritable than at any other time of the menstrual cycle.

Before continuing, it may not be amiss to raise a question that has no doubt occurred in the minds of many. Is it possible, one would like to know, that contractions which are maintained chiefly by the action of estrin could have any appreciable power or force? Fortunately this question may be answered in the affirmative, as the result of a recent though, as yet, brief report by Moir to the Edinburgh Obstetrical Society this year.<sup>17</sup> Moir recorded contractions from the nongravid human uterus *in situ* on selected days of the sex cycle and found that the measurable pressure developed by the uterus at the time of men-



strual bleeding considerably exceeds the expulsive force of uterine contractions occurring in the second stage of labor.

Although the foregoing evidence from human uteri is obtained directly, it is not wholly satisfactory since it lacks the added support of controlled experiments in the nature of replacement therapy in castrated individuals. The complete dependence of human uterine muscle upon estrin for coordinated contractions remains, therefore, to be directly established. However, because of the necessity of estrin for coordinated contractions in the rabbit, and because the human uterus is most active in the follicular phase of the cycle, it seems reasonable to infer that the identical hormone in the human being plays a rôle similar to that which it plays in the rabbit.

*Estrin Production During Pregnancy.*—If the theory advanced by Jeffcoate is to be regarded as plausible, it is essential that the presence of estrin be demonstrated in the human being at the time of parturition. Fortunately such evidence is at hand, not only from the human being but from certain animals as well (mare, cow, monkey, ape). The most familiar data in this connection are those of Zondek which indicate that during the first three months of gestation, estrin excretion rises rapidly, and continuing to rise slowly, it reaches a level at the time of parturition which is not approached or even equaled at any other time in the life of a normal individual.<sup>18</sup> Runge, Hartmann and Sievers, in fact, have recently made detailed studies and find a sharp increase in estrin excretion and production, in the few weeks preceding parturition.<sup>19</sup> By the fourth day of the puerperium, however, the excretion precipitously drops so that the estrin excreted is near pre-pregnancy levels.

Frequent mention has thus far been made of Jeffcoate's paper entitled "The Relation of Estrin to Abortion and Parturition," and I refer to it now in some detail for the point under consideration. This investigation includes, among other things, an account of twelve patients who showed atypical Aschheim-Zondek responses. The findings with the urine of these patients were characterized not by the usual corpora hemorrhagica response which is typical of positive pregnancy diagnosis in mice, but by the presence of distended and hyperemic uteri with no gross evidence of ovarian stimulation. The cause of this, Jeffcoate feels, is attributable to the presence of relatively large amounts of estrin. "We concluded," writes the author, "that these effects were due to the presence of a relative excess of estrin over Prolan A and B in the urine which was injected. The remarkable feature was that the patients whose urine gave the modified reaction almost invariably aborted, or passed a macerated fetus, soon afterward. So intimate was the relation between the urinary findings and the subsequent clinical history of the patients, that we were able in several to forecast that abortion was about to occur, or that the fetus was dead and

the pregnancy likely to terminate." Jeffcoate also reminds us that even after castration in early pregnancy in the human being, estrin is elaborated in amounts indistinguishable from that of normal pregnancy.

*The Nature of Uterine Contractions During Labor.*—Thanks to the direct observations of Rudolph and Ivy<sup>20</sup> in the rabbit and dog and of Ivy, Hartman and Koff<sup>21</sup> in the monkey, sound generalizations may be made concerning the behavior of the uterus in labor.

These investigators find, from observation at laparotomy, that labor progresses only so far as the coordination of uterine activity increases, by establishment of sharply delimited regions of contraction-initiation. After a detailed account of this they summarize as follows: "The process of evacuation of the uterus is the most interesting physiologic evacuation process we have observed to occur in the mammalian organism. The coordination and purposefulness with which its musculature functions and the 'timing' of the sequence of events is very remarkable." Previously they had pointed out, as indeed had others before them, that one finds motility of the feeblest sort earlier in gestation, with no semblance of coordinated contractions.

In view of these findings it would appear to be more than a mere coincidence that estrin, which is endowed with the property of bringing about coordination of contractions, is so abundantly elaborated preceding and up to the time of parturition. Especially is this so since parturition is clearly characterized by coordinated activity of the uterus as a whole.

#### DISCUSSION

There are several questions relating to the theory advanced by Jeffcoate which should be considered before the matter is concluded in our discussion. It has been mentioned, for instance, that estrin is found in considerable amounts during almost the whole of pregnancy, yet it is only in the very last few weeks that coordination of uterine contractions takes place. One would like to know, therefore, why gestation continues in the face of large amounts of estrin.

A full answer to this question cannot be given at the present time. We know, however, from the work of Knaus with the uterus in vitro and subsequently confirmed by other workers with uteri in vivo as well as excised, that the corpus luteum hormone, progesterin, is endowed with the property of inhibiting uterine contractions. In recent years some investigators have expressed doubt as to whether the lutein hormone responsible for inhibition of uterine contractions is identical with the endometrial proliferating hormone, progesterin. In some very recent work, as yet unpublished,<sup>22</sup> it has been definitely established that pure crystalline progesterin not only induces full endometrial growth but inhibition of uterine activity as well.

A further question arises in this connection, however. Pregnancy in the human being continues when castration is performed after the third month, even though the corpus luteum is removed. In these cases the excretion of estrin continues unimpaired. Since the elaboration of progesterin by any structures other than corpora lutea has not been conclusively shown, it is a moot point as to what the stabilizing agencies are which permit the continuance of gestation after castration at this time in the human being. It is possible that the placenta elaborates progesterin, since approximately 10 rabbit units of this hormone may be extracted from a full-term human placenta.<sup>23</sup> It is also possible that the gonadokinetic hormone, prolan, which is present from early pregnancy to the end, may exert a quieting effect upon the uterus. This fact has been undeniably established for the rabbit.<sup>24</sup> In any case, this line of thought compels one to look upon the continuance of pregnancy as being due to a balance of antagonistic hormones circulating in the blood stream throughout nearly the whole of pregnancy. Estrin, on the one hand, favors rhythmicity and co-ordination of uterine activity, while progesterin and possibly some other hormone or hormones tend to counteract the stimulating effect of estrin. It would appear, therefore, that the crux to an understanding of the immediate cause of the onset of labor lies in an appreciation of the factor or factors, extrauterine or intrauterine, which so supplement the action of estrin that it overcomes the restraining influence of the inhibiting agents which affect the uterus.

Among the intrauterine factors suggested there is the consequence upon the irritability of the uterus of the growing fetus, and its associated structures in overcoming the mechanical restraint of the closed womb. It is a physiologic certainty that the great increase in length of the uterine muscle fibers serves to enhance both the irritability and the efficiency of the uterine contractions.

Not only the distention but the shape of the distended uterus may also be important for uterine evacuation as suggested by Laferty. He writes:<sup>25</sup> "If the shape of the normal uterus is kept in mind it is easy to see how it may be a factor in determining the time when engagement of the presenting part occurs, because during pregnancy the intermittent contractions of the uterus can exert no expulsive force on the fetus as long as it is surrounded by amniotic fluid. . . . It is only when the increasing size of the fetus near term causes the presenting part to come in contact with the converging walls of the uterus . . . that the force of the uterine contractions is exerted on the fetus and tends to force it into the pelvic inlet."

A brief summary of the points developed in the foregoing discussion may be stated as follows: Under the influence of estrin, the contractions of the uterus become increasingly coordinated and powerful, in the latter part of gestation. Until this time the hormonal influence

of estrin is held in abeyance by virtue of the antagonistic action of the lutein hormone, progesterin, and possibly other hormones (prolan) as well. As the ovum grows, uterine contractions become increasingly efficient, owing to the coordinating action of estrin and the marked degree of uterine distention. Later the uterine contractions become effective in expulsive force due in part at least to the shape of the full-term uterus. One is tempted to postulate as a consequence of these considerations that the onset of labor may be determined by the time during gestation when the coordinated expulsive forces enumerated above exceed the total restraining hormonal and mechanical intrauterine factors which make for the continuance of pregnancy. This statement should be regarded as a working hypothesis at best, in which the generalities are only approximate possibilities.

The importance of the restraining influence to uterine emptying is suggested by the failure of Witherspoon to initiate labor by the administration of theelin near term.<sup>26</sup> The results were negative, but they were based upon observations on so few patients who received such small amounts of estrin in such an uncontrolled manner that the results are of casual interest only and worth nothing experimentally. Presumably labor took place normally at the proper time, if one may say just when that is. An objection of primary importance to this work, however, lies in the fact that only 150 rat units or less of estrin were used, yet the daily excretion alone at that time is a hundred to a thousand times this quantity. It could hardly be expected, then, that such treatment would prematurely modify the course of gestation.

In conclusion, it is fitting that we do as we did at the beginning, and turn to the paper by Barlow written more than fourscore years ago.<sup>27</sup> "At present, we must confess how much is to be learned respecting parturition ere we can explain many of its phenomena. As it is, to what a variety of queries must the candid physiologist at once reply, 'I do not know,' words which should never be difficult of utterance to anyone who feels that a confession of ignorance is a step to its removal, and who is a sincere inquirer after truth."

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## THE PHYSIOLOGY OF MENSTRUATION IN MACACUS RHEBUS MONKEYS\*

### I. INFLUENCE OF THE FOLLICULAR AND CORPUS LUTEUM HORMONES II. EFFECTS OF ANTERIOR PITUITARY EXTRACTS

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**M**ORE is known concerning the menstrual cycle of *Macacus rhesus* monkeys (*Macaca mulatta*) than any of the other lower primates. Space does not permit a review of the rather extensive literature and for this the reader is referred to reports by Corner,<sup>1</sup> Allen,<sup>2</sup> and Hartman.<sup>3</sup>

The purpose of this paper is to report a study of the hormonal factors influencing the development of the uterine endometrium of *M. rhesus* monkeys. The work has extended over a period of five years and forty-six animals have been used in the experiments. In addition to this series it has been possible, through the generosity of my colleagues, to study material from other laboratories. I am indebted to George W. Corner for endometriums taken at definite times of the normal cycle, to Carl G. Hartman for preparations showing the conditions of early pregnancy, and to Edgar Allen for preparations showing the effects of estrin on the uterus of castrated animals.

#### THE INFLUENCE OF ESTRIN ON THE ENDOMETRIUM

*General Effects.*—Several investigators have described the effects of estrin on the endometriums of castrated monkeys, and there seems to be a general agreement that the most noticeable responses are marked mitotic activity, increase in blood and lymph supply, and general growth. Such endometriums present the conditions found normally during the first half of the menstrual cycle and differ from a typical premenstrual endometrium in several important respects. The uterine

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glands, under estrin stimulation, tend to be straight and, at most, are only slightly coiled (Fig. 1). The epithelium of the glands and uterine lumen may show signs of secretion but are never frayed by such activity as is so characteristic of the condition associated with a corpus luteum. Such epitheliums are usually from 35 to 40 micra in thickness. The nuclei of the glandular mucosa are situated in the basal two-thirds of the epithelium while those of the surface mucosa are usually more generally distributed throughout the thickness of the epithelium, some nuclei may touch the outer surface, while in both, nuclei may be in contact with the basement membrane. These characteristics are quite different from those present during the lutein phase of the cycle which will be discussed later.



Fig. 1.—Uterus of castrated sexually mature monkey which had received 1,080 R.U. of estrin equally distributed over twenty-six days. A typical estrin effect.  $\times 7$ .

A rather conspicuous effect of estrin, when given in large doses, is the development of a clear zone, below the epithelium of the uterine lumen, as seen in histologic preparations (Fig. 1), and in certain instances along the necks of the glands. This area seems due to a local edema of the submucosal tissues and the absence of blood vessels. It has been found only where estrin was administered in large amounts over an extended period, so it may represent a hyperstimulation. At least it is a characteristic estrin effect and is not found in endometriums subjected to the action of corporin.

These responses are such constant results of estrin treatment and check so admirably with the normal condition during the first half of the menstrual cycle that it seems safe to speak of such as follicular or estrin endometriums.

## ESTRIN AND UTERINE BLEEDING

It is a familiar gynecologic observation that oophorectomy, lancing of large follicles, or removal of functional corpora lutea, especially during the middle or latter half of the menstrual cycle, is followed by uterine bleeding within the next few days (Pratt,<sup>4</sup> and others). Experimental work has shown this to be true also for *Macacus rhesus* monkeys (Allen,<sup>5, 6</sup> Van Wagenen and Aberle<sup>7</sup>). Thus it is evident that postoperative bleeding may follow the ablation of either follicles or corpora, and consequently, raises the question as to the source of the factor responsible for the inhibition of menstruation. At the present time there are two ovarian hormones which are known to have definite physiologic effects on the endometrium, namely, estrin and corporin, and it is possible that either one or both of these secretions may be instrumental in inhibiting uterine bleeding. Both of these possibilities will be dealt with in the course of the discussion but first let us consider the effects of estrin.

Our present knowledge of the action of estrin on the monkey endometrium leads one to conclude that the dosages employed in previous studies were in most instances small and the duration of treatment rather brief. Certain important differences are brought out when estrin stimulation is continued over an extended period and at a high level. Monkey 6, for example, received 1,220 R.U. in thirty-one days and during the last twenty days of this period she was given 40 R.U. daily. On the thirty-second day the dosage was reduced to 20 R.U. and while a like amount was given on the thirty-third day, pronounced bleeding started in the evening and continued for four days. A second treatment of the same animal gave similar results. It has also been found that the amount of estrin injected may be increased without precipitating bleeding or the dosage greatly decreased during the first few days without effect, but after prolonged treatment lowering of the dosage is followed by bleeding. It seems that within certain limits the greater the estrin stimulation over an extended period the sooner will bleeding follow discontinuance of treatment, and the more sensitive does the endometrium become to a decrease in dosage and the more profuse is the flow.

The opinion of Morrell<sup>8</sup> and coworkers that there is no correlation between dosage and onset of bleeding or duration of menstruation seems well founded on ample data for experiments of short duration but does not seem true for experiments which extend over several weeks. Under such conditions bleeding may follow within two days after the injections are discontinued and the flow is usually more profuse but of no longer duration than that induced by a six-day treatment. It seems that both dosage and length of treatment are important factors, but the relative importance of each has not been adequately studied to form an opinion.

From this and the results of others it seems that a given dosage of estrin can be administered for twenty to twenty-five days and that bleeding as a rule does not occur during the time of treatment. We have found, however, that if estrin in large doses (40 R.U. or more daily) is injected for longer than about thirty days, bleeding may occur during the experiment. Animal Al. 16, after castration, was given 40 R.U. daily and bleeding started on the fortieth day of treatment. Monkey Al. 28, which had been castrated twenty-seven days previously, was given 80 R.U. daily for one hundred and three days. Bleeding started on the twenty-ninth day and lasted eight days. The uterus was biopsied on the one hundred first day (Fig. 2) and a second

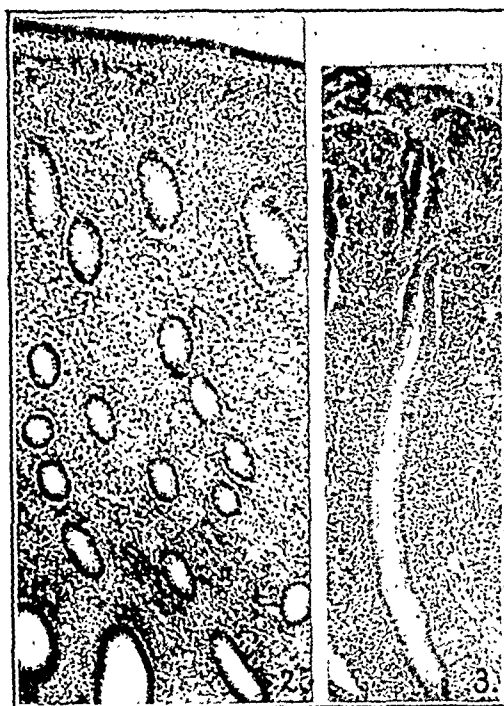


Fig. 2.—Endometrial biopsy of a subadult castrated monkey (monkey Al. 28) which had received 80 R.U. of estrin daily for one hundred and one days. Bleeding occurred on the twenty-ninth day of treatment and continued for eight days. Notice clear zone below surface epithelium. Estrin effect.  $\times 70$ .

Fig. 3.—Endometrium of a subadult castrated monkey (monkey Al. 28) which bled on the one hundred and third day while receiving 80 R.U. of estrin daily. Shows typical condition of "follicular bleeding."  $\times 70$ .

bleeding began on the one hundred third day (Fig. 3). These endometria in all essentials, show a characteristic estrin reaction, and it may be added that no indications of a "Swiss cheese" condition were found.

Why bleeding should occur during prolonged estrin treatment is not known, yet chronic estrin stimulation produces certain peculiarities. The thin endometrium of a castrated animal grows very rapidly under estrin stimulation but soon reaches a thickness beyond which it does not go even though the injections are continued. The minimum dosage and the time required to elicit the maximum response is not



known, but it has been found that 40 R.U. daily is just as effective as 80 R.U. as judged by the thickness of the endometrium on the twenty-fifth to the thirtieth day. When bleeding occurs during a continued estrin treatment, the tissue lost does not seem to be replaced at least to the extent of restoring the original thickness of the endometrium. For example, the endometrium of Al. 28, which was given 80 R.U. daily and which bled on the twenty-ninth day of a one-hundred-three-day experiment, was only 2,160 micra thick on the one hundred third day, while Al. 27, which was comparable in size and sexual development, had an endometrium 4,140 micra thick when given 40 R.U. daily for thirty-two days. Histologic examination of such uteri shows that mitotic activity is more pronounced at the beginning of treatment than after the endometrium has attained its full growth at which time cell divisions are comparatively few.

It also was noticed in several instances that a decrease in estrin was followed by the appearance of white blood cells in the vagina and when the dosage was restored to the original level or above they would disappear. This, however, was not true for red blood cells. After bleeding had once started the period of flow remained within the limits of normal variation, though in some instances it seemed less in amount. The action of estrin on the endometrium suggests certain quantitative aspects, one of which is the occurrence of bleeding as a result of decreasing the dosage after a prolonged treatment. This observation suggests that a condition is established characteristic for a given dosage and that estrin stimulation must be continued at that level to maintain the endometrium and prevent bleeding. Whether or not we can speak of endometriums in terms of rat units of estrin must, however, be determined by a larger series of observations than are now available.

Postoperative menses which follows bilateral castration, especially when performed during the first half of the cycle, can be inhibited by estrin. If the ovaries are removed during the last half of the cycle, when a well-developed corpus is present, large doses of estrin may not successfully inhibit bleeding. This suggests that as the endometrium is modified toward the premenstrual condition, it becomes progressively more difficult to prevent degeneration by the injection of estrin following castration and consequent corporin removal. Additional evidence of this is shown in cases of experimental luteinization of the ovary. For example, the ovaries of animal Al. 28 were luteinized by injections of large doses of a preparation from pregnancy urine, following follicular development produced by anterior pituitary treatment, after which the ovaries were removed and 100 R.U. of estrin given daily. This dosage of estrin, and even less, has been found sufficient to inhibit postoperative bleeding following castration during the first half of the cycle, yet, in this case bleeding oc-

curred on the afternoon of the third day of estrin treatment. Smith (personal communication), by a different technic, has also shown that bleeding from a premenstrual endometrium following cessation of corporin injections is not inhibited by estrin. Monkeys which had received follicular stimulation as a result of injecting pituitary extracts were castrated and given prolonged corporin treatment, after which they bled even though estrin was substituted.

Whether it is possible to restore a premenstrual endometrium to the condition of the follicular half of the cycle by estrin treatment, or at what degree of corporin modification the involution and bleeding of the endometrium can no longer be inhibited by estrin is not known. These observations, however, seem to have a bearing on the question as to why the increase of estrin in the blood during the last week of the human cycle (Frank<sup>9</sup>) does not inhibit the impending menstruation.

#### EFFECTS OF CORPORIN ON THE ENDOMETRIUM

One of the characteristics of the menstrual cycle is the marked modification of the uterine endometrium, associated with the formation of a corpus luteum, resulting in the establishment of a premenstrual condition. Attempts were made to elicit these endometrial changes in castrated monkeys by substitution therapy and to determine the condition under which they can be produced. The procedure followed in general was to remove the ovaries near the middle of intermenses and continue the cycle by administering corporin, or by injecting estrin for a period of days after castration followed by corporin. The endometrium in either case was of the follicular hormone type at the beginning of corporin treatment. This procedure was based on previous observations (Hisaw and Leonard<sup>10</sup>) that corporin produces its characteristic effects on the endometrium after follicular stimulation.

The effects of corporin on the endometrium are first noticeable in the surface epithelium lining the uterine lumen and in the necks of the glands, and the initial modification involves a noticeable elongation of the cells. Under follicular stimulation these structures are about 30 to 40 micra in thickness, while after corporin stimulation, they are usually from 50 to 70 micra thick. This change is followed closely by a rearrangement of the nuclei which is more pronounced in the glands than in the surface epithelium. The nuclei, under estrin influence, are situated mostly in the basal half of the cells some of them touching the basement membrane. Under corporin stimulation the nuclei retreat from the basement membrane leaving a conspicuous clear zone and, particularly in juvenile animals, may become arranged in a double or single row when seen in sections. The basal clear zone may also appear in the surface mucosa though it is usually less well formed, being found only in places. These conditions, as previously men-

tioned, appear first next to the uterine lumen and progress toward the muscularis mucosa and represent a presecretory stage (Figs. 4, 5, and 6).

These modifications are followed by secretory activity which also begins in the necks of the glands and progresses basalward. Secretion is initiated by the appearance of secretory products in the distal ends of the cells and is associated with Golgi activity, which will be described later by Dr. Bilstad. The surface mucosa takes a less conspicuous part in secretion, and under prolonged corporin stimulation, usually is reduced to a thin membrane about 6 to 18 micra in thickness. Due to the gradual progression of corporin effects, it is possible to find all conditions in a single gland from active secretion and fraying in the neck region through primary swelling to unmodified mucous membrane at the base.

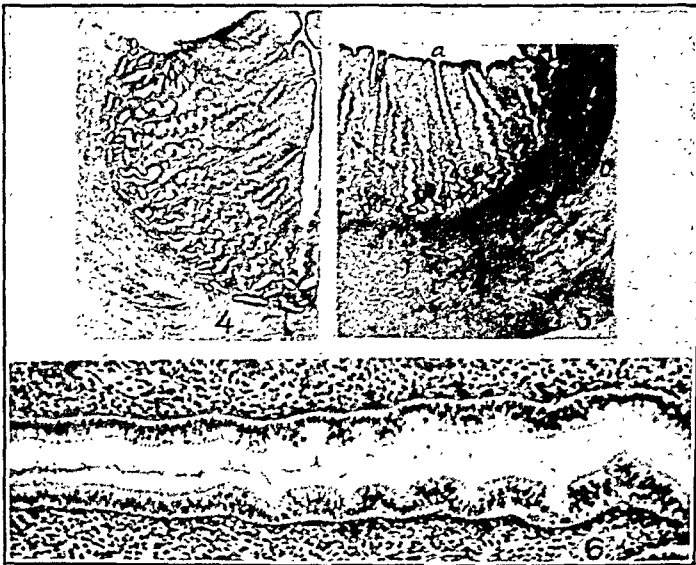


Fig. 4.—Endometrium of a sexually mature monkey (monkey 5) which was castrated on the seventeenth day postmenses, bleeding inhibited for eight days by 35 R.U. of estrin daily, followed by approximately 4 Rb.U. of corporin daily for eight days. Killed at end of sixteenth day. Presecretory corporin effect.  $\times 8$ .

Fig. 5.—Endometrium of juvenile monkey (monkey Al. 4) in which follicular effects were induced by subcutaneous injections of an extract of sheep anterior pituitary powder equivalent to 0.5 gm. daily for sixteen days, followed by castration and injection of approximately 4 Rb.U. of corporin daily for six days. Presecretory corporin effect.  $\times 8$ .

Fig. 6.—High power of a portion of gland *a* shown in Fig. 5. Notice basal clear zone between nuclei and basement membrane. This is a typical presecretory corporin effect and is normally associated with a young corpus luteum.  $\times 90$ .

Coiling and dilatation of the glands are also commonly considered typical corpus luteum effects. Some slight coiling may occur during follicular stimulation but is much more pronounced after corporin treatment. It also seems that spiraling of the glands, under experimental procedure, is correlated to some extent with thickness of the endometrium and consequently length of the glands. The coiled condition may be due to an unequal hypertrophy of the mucosal cells. The cells most strongly affected occupy a spiral position around the gland similar to a winding stairway, and it seems their enlargement

plus the inability of the gland to elongate could be considered a mechanical explanation for their condition as seen in an early premenstrual endometrium. Dilatation is associated with coiling and may occur in short glands that do not show spiraling, and when pronounced, as in strong corporin stimulation, the spiraled appearance may be obliterated, and the walls when widely separated present a "saw-toothed" condition when seen in longitudinal section (Fig. 21).

#### CORPORIN EFFECTS ON ENDOMETRIUM AFTER CASTRATION ATROPHY

It was found in a previous study (Hisaw and Leonard<sup>10</sup>) that corporin could not transform the rabbit endometrium, after castration atrophy, into a progestational condition. Whether or not this is also true of the monkey seemed of interest. Monkey 12, an adult whose menstrual history was known, was castrated and used in an experiment requiring prolonged estrin treatment, after which the uterus was permitted to involute for ninety-seven days and was then removed and used as control material showing castration atrophy. The endometrium of this uterus is about 900 micra thick. The glands are relatively few and straight with a nonsecretory epithelium 18 to 24 micra in thickness. The surface mucosa is also about 18 to 24 micra thick. The nuclei, both here and in the glands, are distributed from basement membrane to surface as a result of the small amount of cytoplasm, and mitoses were not observed (Fig. 7). This condition differs in several respects from that found in normal sexually immature animals. The endometriums of three immature monkeys (Al. 20, O<sub>1</sub>, O<sub>2</sub>) measured 700, 650, and 1,100 micra in thickness, the surface epithelium about 36 micra, and the glandular epithelium 30 to 36 micra. The diameter of the glands is about the same as that of the castrated condition, 100 to 120 micra. The stroma, after castration atrophy, is dense with closely packed, deeply staining, connective tissue nuclei which, when spherical, are about 6 micra in diameter. In the immature animal the stroma is not so dense and the nuclei, when round, are about 9 micra in diameter with chromatin more diffuse. The immature endometrium differs histologically from that of a castrated animal, in that the surface and glandular epithelium is thicker, the stroma is less dense with larger nuclei containing reticular chromatin, and the presence of an occasional mitotic figure. It can be concluded from this that the immature ovary does influence the endometrium.

When corporin is administered after castration atrophy, definite modifications of the endometrium occur as shown by the following experiments. Two juvenile monkeys (Al. 13 and Al. 24), which were first used for other experiments, were castrated and after thirty-seven and thirty-eight days were given 4 Rb.U. of "estrin-free"\* cor-

\*Six rabbit units of the corporin preparation used did not produce cornification or mucification of a castrated rat's vagina when standardized for estrin.

porin daily for ten days. The endometria of both show definite corporin effects. The endometrium of Animal Al. 24, which gave the better response (Fig. 8), is about 2,000 micra thick, the glandular epithelium is 30 micra thick in the neck region and over 60 micra at the base, while the diameter of the glands range from 90 to 120 micra in the neck region to 210 to 270 micra at the base. The surface epithelium is very thin being like that seen just previous to normal menstruation or after prolonged corporin treatment. The endometrium of Animal Al. 13 is similar though not so well advanced. The chief difference being the thickness of the surface epithelium which is 42 micra thick, actively secreting and has the characteristic clear zone between the basement membrane and nuclei. The glands of both

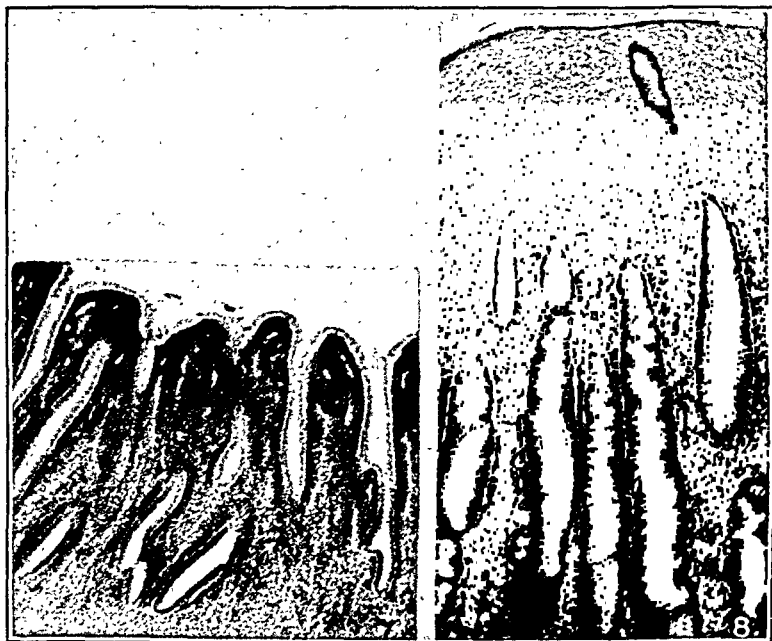


Fig. 7.—Endometrium of an adult monkey (monkey 12) after ninety-seven days of castration atrophy.  $\times 60$ .

Fig. 8.—Endometrium of a juvenile monkey (monkey AL 24) which was castrated and thirty-eight days later given 4 Rb.U. of "estrin free" corporin daily for ten days. Mild though definite corporin effects.  $\times 55$ .

animals are dilated and show some signs of coiling, with thickening of the epithelium and mitoses common in the basal portion.

The stroma, in general, is much more reticular than that seen in the immature or castrated condition though the connective tissue cells in certain areas immediately below the surface mucosa, especially in Animal Al. 13, seem enlarged giving a dense appearance due to accumulation of cloudy cytoplasm. The nuclei, however, have about the same diameter as those seen in the immature endometrium, about 9 micra, and the chromatin is diffuse.

From these observations it may be concluded that corporin can produce its characteristic reactions in an endometrium which has un-

dergone castration atrophy. The effects, however, seem limited mostly to the structures existing at the beginning of treatment. Though mitotic activity is present it is not as extensive as that seen after administration of estrin. The function of estrin in this reaction seems chiefly that of furnishing structures on which corporin can act and not that of sensitizing the tissues so they can respond to corporin.

#### INHIBITION OF UTERINE BLEEDING BY CORPORIN

Smith and Engle<sup>11</sup> have found that at least under the conditions of their experiments, corporin will inhibit menstruation. The corporin preparation used by Smith and Engle contained one rat unit of estrin for each 19 gm. equivalent of corpus luteum tissue. We have been able to repeat these experiments with a corporin preparation which contained less than one rat unit of estrin for each 375 gm. equivalent of lutein tissue (7.5 Rb.U.). When 4 Rb.U. of this preparation were administered daily, the endometrium was transformed into a definite corporin condition by the tenth day (Fig. 9), and by the eighteenth (Fig. 10) to the twenty-fourth day (Fig. 11) many of the glands showed signs of secretory exhaustion without any indications of impending menstruation.

This action of corporin was also shown by its ability to inhibit bleeding after discontinuance of an extended estrin treatment. Monkey Al. 16, which was also used in other experiments, was castrated and given 40 R.U. daily for twenty-four days, after which she received 4 Rb.U. of "estrin-free" corporin daily for twelve days. On the last day of corporin treatment and the four succeeding, 100 R.U. of estrin were administered daily. Copious bleeding occurred on the morning of the fifth day. Bleeding occurs within a very few days on withdrawal of estrin after prolonged treatment, so it seems quite obvious that corporin exercised an inhibitory effect, and also we may again conclude that estrin, at the dosage employed, was not able to prevent involution of the premenstrual endometrium developed.

There is some indication that the threshold dosage of corporin required to inhibit menstruation after estrin treatment is higher than that for modification of the endometrium. Several animals (Animals 2, 6, 9, and Al. 11) bled while receiving corpus luteum extract in small doses. Monkey 2 showed no corporin effects. Monkey 6 was given two series of corporin injections following prolonged estrin treatments and when the uterus was examined at the end of the second experiment, at the first appearance of bleeding, there seemed to be slight premenstrual changes. Postoperative menstruation was inhibited by estrin in Animal Al. 11 and bleeding occurred on the fifth day of corporin treatment associated with definite corporin effects. A young

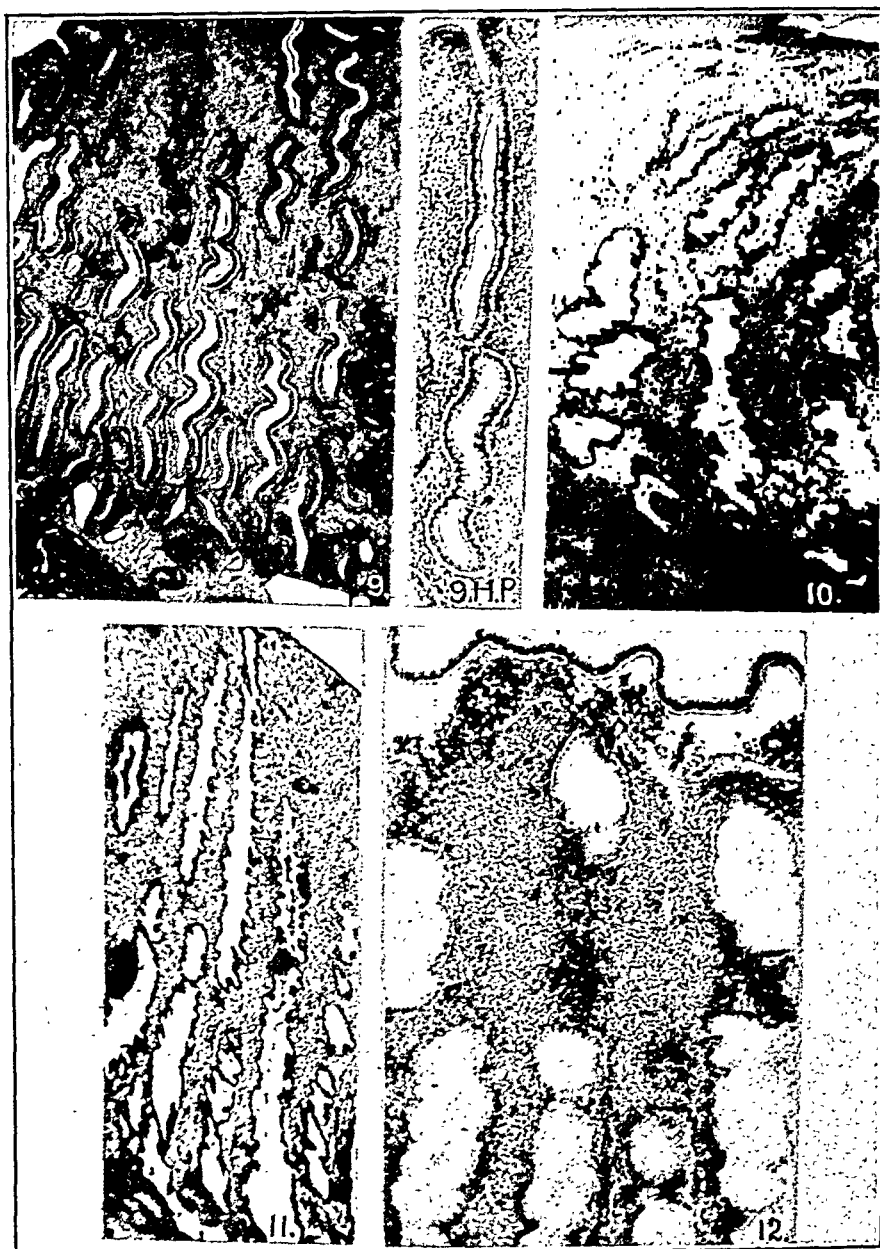


Fig. 9.—Endometrium of a juvenile monkey (monkey Al. 19) in which follicular effects were induced by subcutaneous injections of sheep anterior pituitary extract equivalent to 1 gm. of powder daily for sixteen days, and was followed by castration and the injection of 4 Rb.U. of corporin daily for ten days. Presecretory corporin effect.  $\times 30$ . High power  $\times 60$ .

Fig. 10.—Endometrial biopsy of a young adult monkey (monkey Al. 17) which was given a similar treatment as that described for Fig. 9, except the corporin injections were continued for eighteen days. Glands actively secreting. Premenstrual condition.  $\times 30$ .

Fig. 11.—Endometrium of animal described in Fig. 10 after twenty-four days of corporin treatment. Glands show secretory exhaustion.  $\times 30$ .

Fig. 12.—Endometrium of an adult monkey (monkey 9) castrated eighteen days postmenses, received a total of 4,250 R.U. of estrin during the next six days, followed by about  $\frac{1}{2}$  Rb.U. of corporin daily for eight days. Killed at end of fourteenth day. Young corpus luteum found in the right ovary at time of castration. Corporin effects and beginning bleeding.  $\times 60$ .

corpus was found when Animal 9 was castrated, postoperative bleeding was successfully inhibited by estrin, and when killed fourteen days later, after seven days' corporin treatment, the endometrium showed a marked corporin reaction and impending menstruation (Fig. 12). It seems probable that the animal's own corpus had produced some endometrial modification before castration, and though it is not known what effect estrin has on such endometria, it seems improbable that such an advanced premenstrual condition could have been produced without corporin treatment. The minimal dosage of corporin required to produce changes in the endometrium has not been determined nor is the minimal dosage for the inhibition of menstruation known. Neither is the maximal degree of corporin modification known beyond which it becomes difficult or impossible to inhibit bleeding by administering estrin. Definite conclusions must, therefore, await the results of experiments devised especially to settle these points.

#### SIMULTANEOUS ESTRIN AND CORPORIN TREATMENT

It has been found (Leonard, Hisaw and Fevold<sup>12</sup>) that when estrin and corporin are injected simultaneously into rabbits castrated during estrus, the uterine response depends on a quantitative relationship between the two hormones. That is, 10 R.U. of estrin about balances 1 Rb.U. of corporin, and the reaction can be thrown in either direction by varying the dosage of hormone. This proportionate relationship between estrin and corporin (10 R.U. to 1 Rb.U.) does not seem to hold for the monkey.

Monkey 11 received 40 R.U. of estrin daily for twenty-two days followed by a combination of 50 R.U. of estrin plus 4 Rb.U. of corporin per day for three days and 73 R.U. plus 4 Rb.U. for seven days. When the endometrium of this animal (Fig. 13) is compared with that of Animal Al. 19 (Fig. 9), which received 4 Rb.U. of corporin alone daily for ten days, after follicular stimulation, it is seen that they show about the same corporin effects. The only noticeable difference is the glandular mucosa of Animal Al. 19 is more actively secreting than that of Animal 11. Animal Al. 23 was given 40 R.U. of estrin daily for twenty-four days followed by 100 R.U. of estrin plus 2 Rb.U. of corporin daily for ten days. This endometrium also shows a marked corporin response comparable in degree to Animals Al. 19 and 11. All three of these endometria show much better corporin effects than that of Animal Al. 22 which received 4 Rb.U. of corporin daily for five days following follicular stimulation and castration (Fig. 14).

Monkey Al. 29 received 40 R.U. of estrin daily for seventeen days followed by a combination of 100 R.U. of estrin plus  $\frac{1}{2}$  Rb.U. of corporin daily for ten days. The epithelium of the uterine lumen and glands is of about the same thickness as found after estrin injections, but the glands are dilated and the clear zone in the stroma below the surface mucosa, so characteristic of estrin action, is absent. This suggests that estrin may have prevented the action of corporin on the epithelium of the glands and uterine lumen but did not inhibit dilatation of the glands or elimination of the surface clear zone.



Monkey 7 was given 40 R.U. of estrin daily for twenty-six days, and during the last twelve days of this period, she also received  $\frac{1}{6}$  Rb.U. of corporin daily. This endometrium shows a distinct estrin condition, yet, it is not known that this dosage of corporin would produce modifications if given alone.

When estrin and corporin are given simultaneously for an extended period the uterus attains a larger size than when the two hormones are administered singly. A sexually immature castrated monkey (Al. 33) which received 2 Rb.U. of corporin plus 300 R.U. of estrin daily for twenty-five days had a uterus measuring 22 by 22 mm. in breadth and thickness at the fundus. The uterus was soft and the endometrium very thick. The glands showed secretory exhaustion and many were greatly dilated. The vaginal smear and the sexual skin were not typical for an animal receiving so much estrin. The vaginal cornification gradually disappeared and the edematous condition of the sexual skin, a characteristic estrin effect in young monkeys, was greatly reduced.

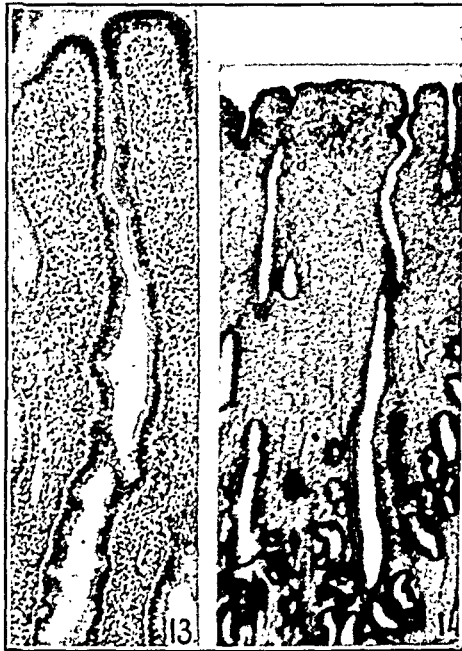


Fig. 13.—Endometrium of an adult monkey (monkey 13) after castration and the injection of 40 R.U. of estrin daily for twenty-two days followed by a combination of 73 R.U. of estrin plus 4 Rb.U. of corporin daily for ten days. Presecretory corporin effect. Compare with Fig. 9 high power. No corpora or large follicles in ovaries at castration.  $\times 80$ .

Fig. 14.—Endometrium of juvenile monkey (monkey Al. 22) in which marked follicular development was induced by a twenty-day treatment of anterior pituitary extract followed by castration and injection of 4 Rb.U. of corporin daily for five days. Mild corporin effect.  $\times 20$ .

Though these experiments do not establish a quantitative corporin-estrin balance, if such exists for the monkey, they do show that corporin can act on the endometrium in the presence of large amounts of estrin. The reason for this marked difference between the rabbit and monkey, with regard to estrin-corporin balance, is not known, but if corporin does facilitate the elimination of estrin, as thought by Smith and Smith,<sup>13</sup> it seems we must conclude that it is more efficient in the monkey than in the rabbit.

## ANTERIOR PITUITARY EXTRACTS\*

The effects of anterior pituitary implants and extracts on monkeys have been reported by several workers (Allen,<sup>14</sup> Hartman,<sup>15</sup> Courier et al.,<sup>16</sup> Saiki,<sup>17</sup> Smith and Engle,<sup>11</sup> Engle,<sup>18, 19</sup> Hisaw<sup>20, 21</sup> et al.),† and it has been the general experience that as a rule follicular growth without luteinization follows subcutaneous treatment. Later it was discovered (Hisaw et al.<sup>22</sup>) that an aqueous pyridine extract of anterior

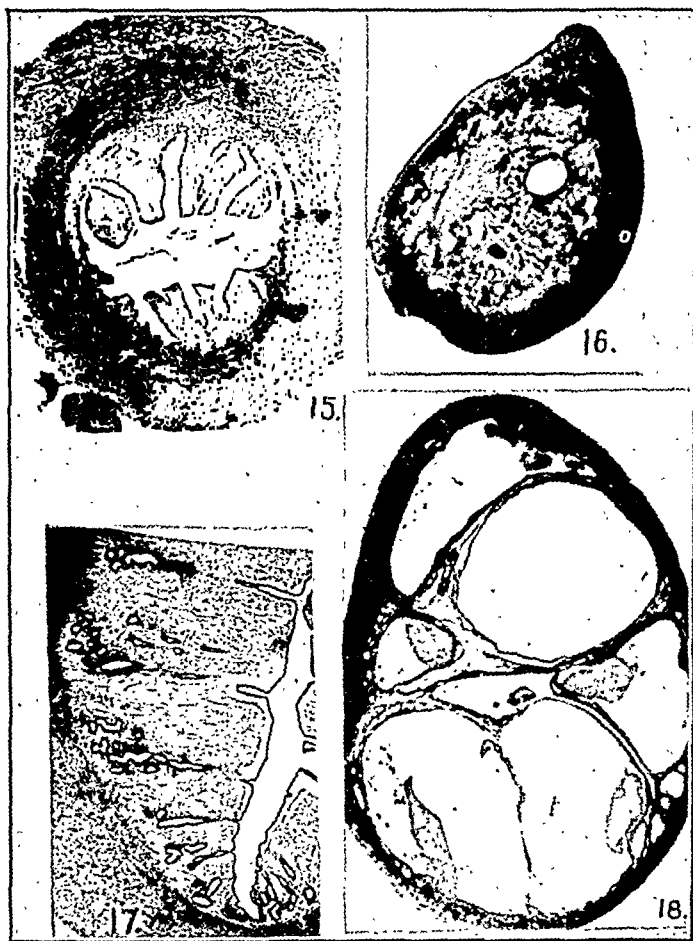


Fig. 15.—Transverse section of the uterus of a sexually immature monkey. Notice the large crypts in the endometrium and basal buds.  $\times 10$ .

Fig. 16.—Section of the ovary of a sexually immature monkey (see Fig. 15).  $\times 10$

Fig. 17.—Endometrium of a sexually immature monkey showing estrin effects associated with follicular stimulation of the ovaries by subcutaneous injections of anterior pituitary extracts.  $\times 10$ .

Fig. 18.—Ovary of a sexually immature monkey showing follicular development induced by subcutaneous injections of anterior pituitary extracts (see Fig. 17).  $\times 10$ .

pituitary powder which produced only follicular development when given subcutaneously would luteinize the ovarian follicles when ad-

\*The anterior pituitary extracts were prepared by the methods used in our laboratory, from pituitary powder generously furnished at different times by the Wilson Laboratories, E. R. Squibb and Sons, and Parke, Davis and Co. An anterior pituitary extract, Prephysin, prepared by Dr. A. E. Meyer of Chappel Bros., also was found satisfactory for this work.

†The reader is referred to the reviews of Smith (1932) and Engle (1932); Chapters XV and XVI, *Sex and Internal Secretions*, Williams and Wilkins, for a general discussion.

ministered intravenously. This observation made it possible to produce the follicular and corpus luteum phases of the menstrual cycle in either sexually immature or adult monkeys. That is, the marked follicular development in the ovaries following subcutaneous treatment is associated with typical estrin conditions in the endometrium, and this can be changed to the premenstrual condition either by injecting anterior pituitary extracts intravenously, and luteinizing the ovaries or by castration after follicular stimulation and the administration of corporin.

The immature endometrium (Figs. 15 and 16) is modified by follicular hormone from the stimulated ovaries. Mitotic activity occurs in both stroma and glandular mucosa causing a thickening of the endometrium and consequently narrowing of the crypts. The distal portions of most of the glands seem to be formed by closing of the crypts while the basal branchings originate from epithelial buds of the sides and bottom. All the chief aspects of such endometria are characteristic estrin effects (Figs. 17 and 18). The clear border underneath the surface mucosa is conspicuous and extends for a considerable distance down the sides of the glands. The glands are not coiled, non-secretory, and the mucous membrane is usually about 36 micra in thickness.

Such endometria will bleed if the pituitary injections are discontinued. The time elapsing between treatment and bleeding and the extent of the hemorrhage depend upon the development induced in the endometrium. The greater the endometrial response the sooner bleeding will occur after treatment and more extensive will be the hemorrhage, but the duration of bleeding does not seem to be affected. The dosage of pituitary extract may be reduced to the point where no external signs of its action on the ovary are noticeable in the sexual skin, yet bleeding occurs on discontinuance of treatment. Such bleeding, however, may not appear before fifteen or twenty days after treatment and is usually detectable only on microscopic examination of the vaginal smears. Bleeding following follicular stimulation is in all cases from an endometrium of an estrin type, and it seems permissible to speak of it as "follicular menstruation."

The estrin type of endometrium associated with follicular development, as a result of anterior pituitary treatment, can be modified to the lutein or premenstrual condition by castration and the injection of corporin. The endometrial changes (Figs. 5 and 6) are in all essentials the same as those described for the effects of corporin on the castrated adult though the glands are not as numerous.

Lutein effects may also be developed in the endometrium when the follicular stimulated ovary is luteinized by intravenous injections of

anterior pituitary extracts (Figs. 19 and 20). Such luteinization is associated with involution of the sexual skin and a decrease in size of the ovaries. The changes in the ovaries themselves involve intra-follicular hemorrhages and formation of lutein tissue, apparently from both the granulosa and theca interna of unruptured follicles.

Our attempts to luteinize the ovaries by intravenous injections were not always successful. Rather crude unfractionated preparations gave the best results while the effects of more purified extracts, from which most of the luteinizing factor had been removed, were consistently negative. A single intravenous injection had no noticeable effect and a luteinizing preparation administered intraperitoneally daily for eight



Fig. 19.—Luteinized ovary of a sexually immature monkey (monkey Al. 9) produced by intravenous injections of anterior pituitary extracts following experimentally induced follicular development.  $\times 10$ .

Fig. 20.—Uterine biopsy of Monkey Al. 9 showing endometrial condition associated with the luteinized ovary described in Fig. 19. Presecretory lutein effect.  $\times 30$ .

days neither produced corpora nor prevented involution of the ovaries and bleeding. One monkey which had excellent follicular development was given extract equivalent to 400 mg. of luteinizing powder intravenously in two doses twelve hours apart and when killed three days later showed only one small blood follicle. One milligram of this substance is sufficient to produce marked luteinization of a rat's ovaries under similar circumstances. Not only do these observations emphasize the difficulty of luteinizing the monkey ovary, in contrast to other laboratory animals, but also suggest the possibility that a pituitary preparation containing a proper balance between the follicular stimulating and luteinizing hormones is more favorable for luteinization.

## EPITHELIAL PROLIFERATION

Certain animals in these experiments (Animals Al. 9, Al. 10, Al. 11, and Al. 32) showed a peculiar type of epithelial proliferation in the vicinity of trauma resulting from uterine biopsy.

The reaction in Animal Al. 10 was slight, the treatment of Animal Al. 11 was complicated by a series of procedures, but Animals Al. 9 and Al. 32 seem to be clear cases which are favorable for analysis. The luteinized ovaries of Animal Al. 9 were re-

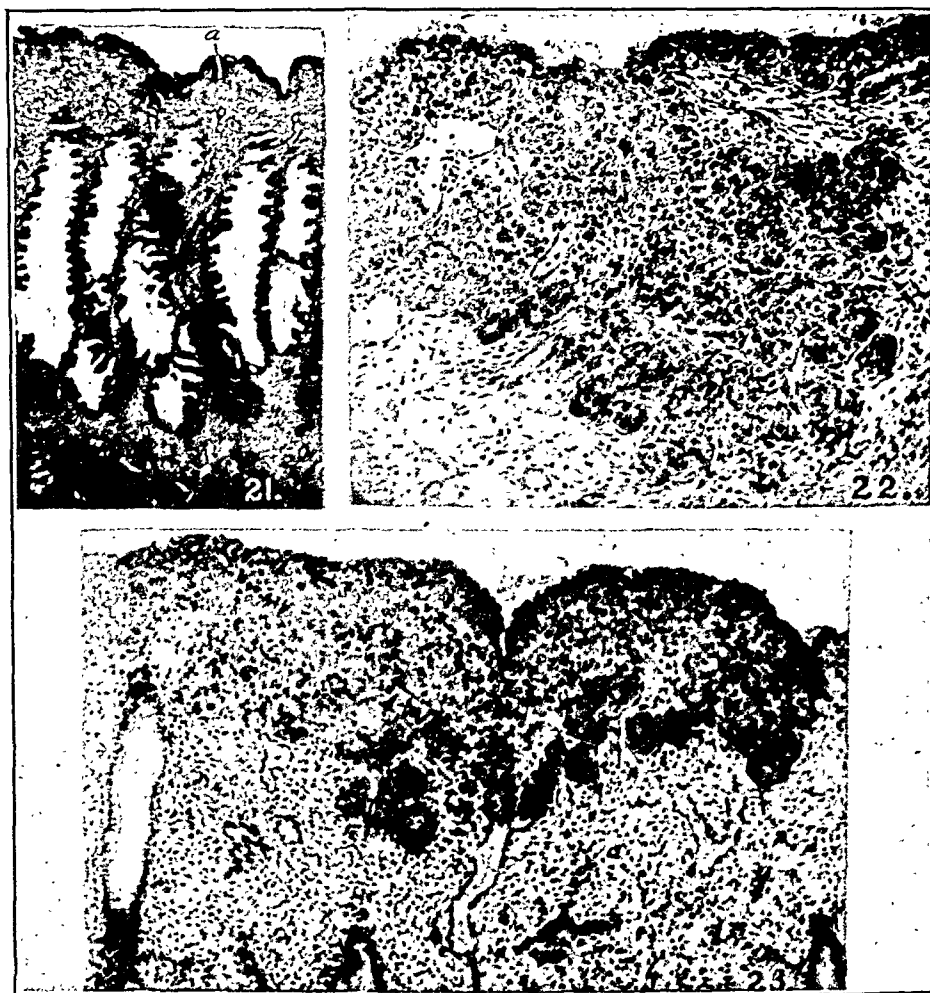


Fig. 21.—Same endometrium as that shown in Fig. 20 after castration, Fig. 19, and the injection of a total of 16 Rb.U. of corporin during the next five days. Secretory corporin condition and epithelial proliferation, shown at *a*, in the region of trauma resulting from the biopsy.  $\times 25$ .

Fig. 22.—Epithelial proliferation of endometrium (monkey Al. 32) produced by (1) follicular stimulation of the ovaries with anterior pituitary extracts; (2) castration; (3) injection of corporin, 25 Rb.U. in eight days; (4) biopsy of the endometrium which was in a presecretory condition comparable to Fig. 20; (5) and continuing the corporin treatment, 4 Rb.U. per day, for five days.  $\times 100$ .

Fig. 23.—Normal implantation site in the endometrium of a monkey ten and one-half days after ovulation. Compare epithelial proliferation with that shown in Fig. 22. Photomicrograph furnished the author by Dr. C. G. Hartman and Dr. G. L. Streeter. (C-419 Carnegie Collection.)  $\times 100$ .

moved (Fig. 19) and a uterine biopsy showed definite corporin effects (Fig. 20). This was followed by corporin injections for five days (16 Rb.U. total) which produced a well-developed premenstrual endometrium and epithelial proliferation

(Fig. 21). Animal A1. 32 was first given pituitary extract subcutaneously which elicited pronounced follicular development. This was followed by castration and the injection of 25 Rb.U. of corporin in the next seven days plus 40 R.U. of estrin during the last three days of treatment. A uterine biopsy taken at this time showed a corporin reaction similar to that pictured in Fig. 20. Following the biopsy, 4 Rb.U. of corporin was administered daily for five and a half days and the animal killed. The endometrial condition at the time of autopsy was comparable to that shown in Fig. 21. Epithelial proliferations in all instances were found only in the traumatic areas and are shown by nests and cords of cells budded off from the surface mucosa and necks of the glands into the neighboring stroma (Fig. 22). The mouths of the glands in places are closed by the proliferated cells while on the "saw-toothed" sides buds originate from the crypt-like depressions and not from the points which extend into the lumen.

There is some doubt as to whether or not these epithelial proliferations should be considered decidual reactions. Decidual cells, so far as known, are of connective tissue origin while these are unquestionably from the mucous membrane. Some idea of their probable significance, however, can be drawn from comparison with the endometrial modifications which occur at the normal implantation site of a fertilized ovum. C. G. Hartman and G. L. Streeter have made it possible for us to study such material by loaning a slide (C-419 Carnegie Collection) which shows the initial changes of the endometrium when an ovum becomes attached and before implantation actually occurs (Fig. 23). The similarity of the normal and the experimentally induced proliferations is very striking. The normal reaction is limited to the area of attachment of the ovum and the experimental to the regions of trauma. The only apparent difference is that the size of the cells in certain areas of the induced proliferations seems greater. The physiologic conditions under which these proliferations occurred were the same as those well established for decidual reactions in laboratory rodents. They were formed while the uterus was under the influence of corporin following a previous estrin stimulation. Traumatization of the uterus while under the influence of estrin or after prolonged corporin treatment did not induce proliferation. Yet, if these structures are to be considered as decidual, it must be conceded that in the monkey the first decidual cells are mucosal in origin and are formed before the connective tissue becomes involved. Also, this may explain the source of nests of certain large epitheloid-like cells in the stroma surrounding the primate implantation site and whose origin has been much discussed. It should be mentioned, however, that these results were rather incidental in experiments devised for another purpose, so should be supplemented by other studies planned specifically for decidual reactions.

#### DISCUSSION

The experiments reported here are not extensive enough to warrant broad conclusions but they do demonstrate that it is possible, by ex-

perimental means, to induce endometrial modifications which appear identical with various stages in the normal menstrual cycle. A more accurate comparison cannot be made at present due to a lack of detailed information concerning the changes during the normal cycle. The results in their broader aspects do show that estrin and corporin each has its specific endometrial effects which are correlated with the follicular and lutein halves of the menstrual cycle. These effects are so characteristic that it is quite easy to distinguish one from the other, even in cases of mild stimulation, which makes it possible to judge the physiologic action of the ovary by studying preparations of the endometrium. Examination of ovaries and their corresponding uteri removed from women at known times of the cycle suggests that these observations may also be applied to human material. Studies of curettage material taken at the time of oophorectomy have shown that it is possible to determine, with surprising accuracy, the physiologic action of the ovaries as evidenced by the condition of the endometrium. It is not implied that any information concerning gross pathology, such as follicular or lutein cysts, can be detected in this way, but only whether or not the endometrium is under follicular or lutein influence. A large number of endometrial biopsies has been studied in cooperation with R. E. Campbell and E. L. Sevringhaus and, though the details will be reported later, it may be mentioned briefly here that it is possible to determine whether or not a rapid follicular growth follows menstruation, whether the cycle is nonovulatory or involves corpora formation, and whether bleeding is from an estrin or corporin endometrium.

The degree of estrin action on the endometrium of the monkey is more difficult to determine, from a diagnostic standpoint, than that of corporin. When estrin is administered (40 R.U. daily) to a castrated animal, there is for the first few days marked mitotic activity in the glandular epithelium which gradually decreases and may be almost absent after thirty days. This condition may have the appearance of a so-called "resting endometrium" even in the presence of estrin. The chief estrin characteristic in such cases is the clear zone in the stroma underneath the surface mucosa, and this may be absent when the estrin dosage is small. The minimum amount of estrin required to produce this clear zone has not been determined. On the other hand the action of corporin is so distinctive that it can be detected easily even though the stimulation is slight. In view of these observations it seems that one may not be able to determine by examining an endometrium, whether or not an extended period of amenorrhea has occurred associated with some estrin action, but if corporin is present in effective amounts, its effects can be seen.

Two factors influencing uterine bleeding seem to be clearly demonstrated in this study. Bleeding which occurs at the termination of a

nonovulatory cycle is apparently due to the involution of the follicular structures resulting in a decrease or cessation of estrin secretion. Bleeding from a typical premenstrual endometrium of an ovulatory cycle seems to be the result of physiologic involution of the corpus luteum. This opinion is based on the experimental observation that corporin is the only substance so far known to form a typical premenstrual or progestational endometrium and the only substance which is able to continue its existence over an extended period. The fact that bleeding may occur in nonovulatory cycles without any noticeable gross changes in the ovaries does not contradict the opinion stated in regard to follicular bleeding. Follicular cycles are apparently due to the failure of pituitary stimulation of the ovaries to progress farther than the follicular half of the cycle. There is no reason to doubt that such ovaries secrete some estrin, and experimentally, it is known that bleeding follows discontinuance of estrin treatment in which rather small doses have been used. The absence of ovulation and corpus luteum formation may be due to failure of secretion of luteinizing hormone as a result of insufficient estrin stimulation of the pituitary. This idea is not without experimental foundation as it has been found by Hohlweg (1934) that estrin injections are associated with excessive luteinization and by Hisaw and Fevold (in press) that such treatment increases the luteinizing ability of the pituitary.

If one should venture an hypothesis at this time to explain the primate cycle, it seems that the following ideas, based for the most part on well-established experimental results, are worthy of consideration. It is probable that the anterior pituitary gradually increases in follicular stimulating ability during the follicular half of the cycle. This is associated with follicular development in the ovaries, and consequently a progressive increase in the secretion of estrin which promotes growth of the endometrium. Estrin, while small in amount, may stimulate the pituitary but as it increases a concentration is reached, shortly before ovulation, which begins to inhibit secretion of the follicular stimulating hormone and stimulate the production of luteinizing hormone. When a proper balance between the two pituitary hormones is attained, preovulatory enlargement of the follicle occurs as a prerequisite for ovulation and luteinization which follows. The fact that the developing primate corpus, as established for human beings, continues to secrete estrin for some time would also tend to intensify the secretion of luteinizing hormone and prolong the lutein half of the cycle. It also seems significant that it is difficult to inhibit the action of corporin on the primate endometrium by large doses of estrin. As the organization of the corpus advances, estrin secretion decreases and as a consequence the pituitary gradually regains its follicular stimulating activity perhaps in a fashion similar to



that following castration. It seems probable that corporin may not act directly on the pituitary, at least in an inhibitory fashion, as the gonad stimulating action of the pituitary increases in the presence of corpora as well as after castration, and the results of corporin administration so far have not been convincing in this regard. With the increase of follicular stimulating hormone and the corresponding decrease in luteinizing hormone, physiologic involution of the corpus ensues, resulting in the cessation of corporin secretion and withdrawal of its inhibitory influence on menstruation and, as a result, the endometrium disintegrates and bleeding follows. The gradual increase in follicular stimulating hormone initiates new follicular development and the cycle is repeated.

#### SUMMARY

Over forty monkeys were used in this series of experiments to determine the physiologic factors responsible for the development of the primate endometrium. The experiments may be divided into two groups: (1) those dealing with the action of estrin and corporin on the endometrium after castration, and (2) those in which endometrial modifications were induced through the action of anterior pituitary preparations on the ovaries. It is possible by both of these methods to produce endometrial conditions typical of the different phases of the menstrual cycle. The estrin effects are characteristic of the first half or follicular part of the cycle and corporin the last half or lutein part. The histologic and cytologic changes produced by estrin and corporin are so different that their individual actions can be easily distinguished.

Postoperative menses can be inhibited by estrin following oophorectomy during the follicular half of the cycle but becomes progressively more difficult with the development of the lutein condition. Attempts to inhibit bleeding of well-developed premenstrual endometria by the injection of estrin were not successful. When estrin is administered for an extended period following castration atrophy of the endometrium there is first marked mitotic activity which gradually subsides and may be almost absent by the end of thirty days. Such endometria will bleed if estrin injections are discontinued or the dosage materially lowered and may even do so during treatment when injections are continued for a long time.

Corporin will inhibit postcastration bleeding of either a follicular or a lutein endometrium and will also inhibit bleeding which invariably follows discontinuance of a prolonged estrin treatment. The dosage required for inhibition of bleeding seems higher than that which produces characteristic corporin effects in the endometrium. When corporin is administered for an extended period, following an estrin

treatment, the endometrium develops the modifications found in the lutein half of the normal cycle, and the glands finally become secretorally exhausted and remain in this condition as long as treatment is continued. Few or no mitoses are found and this is especially true of well-developed premenstrual conditions. Corporin can also produce its characteristic effects, without previous estrin stimulation, in endometriums which have undergone castration atrophy. When corporin and estrin are injected simultaneously  $\frac{1}{2}$  Rb.U. of corporin is at least partially effective in the presence of 100 R.U. of estrin.

Epithelial proliferations from the surface mucosa and distal portions of the glands were found in several instances following traumatization, as a result of biopsy, during the presecretory corporin phase of experimental cycles. These proliferations were not observed to follow biopsies of estrin endometriums or biopsies after prolonged corporin treatment. The significance of these epithelial growths is not definitely known, though they are very similar and appear morphologically identical with those seen at the implantation site of a fertilized ovum.

It is a pleasure to acknowledge the assistance of Dr. H. L. Fevold, Dr. R. K. Meyer, Dr. S. L. Leonard, Dr. Roy Hertz, and Dr. A. A. Hellbaum who have appeared as coauthors on several preliminary reports during the progress of this study.

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## TRAUMATIC NEURITIS IN THE PUERPERIUM

ALVIN J. B. THILMAN, A.B., M.D., New York, N. Y.

*(From the Department of Obstetric and Gynecology, Columbia University)*

**T**RAUMATIC NEURITIS as a puerperal disability has been recognized for a long time. Notwithstanding the fact that it is an aggravating disturbing incident when encountered clinically, it has received little recognition in obstetric textbooks. This neglect may be attributed to the fact that very few cases are met with in the course of a professional lifetime. Furthermore, when so encountered the patient is transferred to the care of the neurologist or orthopedist as the case may be, and so lost to the field of obstetric records.

The causes of paralysis in the puerperium fall into ten groups: (1) Functional (hysterical). (2) Changes produced in the brain (cerebral hemorrhage, massive and petechial; cerebral thrombosis; embolus, from endocarditis and, very rarely, pelvic phlebitis; syphilis; organic disease of any form). (3) Changes in bone (osteomalacia; caries; fracture and dislocation; exostosis, callus; arthritis). (4) Changes in muscles (dermatomyositis; contusion with hemorrhages). (5) Foci of infection. (6) Poisoning by drugs and heavy metals. (7) Infectious diseases. (8) Adjacent inflammatory processes (acute endometritis, tubo-ovarian abscess, salpingitis; thrombophlebitis). (9) Type described by Moebius in 1887 (localized, for which only pregnancy can be held to account; generalized). (10) Trauma of delivery. The present paper will be concerned only with the traumatic type.

The etiology of traumatic paralysis following delivery has been explained on anatomical grounds. Several theories have been offered. Hunermann in 1892 attributed the frequency of involvement of the peroneal nerve alone to its position in the lumbosacral plexus. The lumbosacral trunk, formed by the union of the smaller portion of the fourth and entire fifth lumbar nerve, is situated at its formation on the ala of the sacrum under cover of the psoas; descending into the pelvis it emerges from beneath the psoas and from thence is unprotected. The first, second, and third sacral roots entering into the formation of the sacral plexus lie on the piriformis muscle and are thus unprotected from pressure against the bone. It has been shown (Lefebvre) that the main portion of the peroneal nerve is a continuation of the lumbosacral trunk. The Hunermann theory then considers that the exposure of a portion of the lumbosacral cord, which distally is the peroneal nerve, is responsible for the peroneal palsy. Hunermann's localization of the paralysis in the peroneal nerve has not been corroborated in our cases nor in the majority of those reported.

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88, or 74 per cent. The incidence of spontaneous delivery in this series was 23, or 26 per cent. In view of the pelvic peculiarity, with the added factor of a large baby, it is obvious that instrumentation alone is not required to produce the lesion.

The incidence of traumatic puerperal neuritis is low, but it must be higher than is suspected. At Sloane Hospital there have been only 9 cases among 18,800 deliveries in ten years. We have no doubt that there were a few other cases that escaped notice and ultimately sought the neurologist or orthopedist. Since we have been watching for the cases, however, we have seen 6, with possibly a seventh questionable case.

Pain is the earliest symptom and occurs early in labor. It appears along the course of the sciatic nerve, is not constant at first but becomes aggravated and persistent with uterine contractions. Spasmodic contractions of the extremity occur with the increasing severity of the pain and the limb is held in flexion. Agonizing cramps appear in the calf. With the widespread employment of sedatives, this valuable symptom may escape notice and only in the postpartum period is it evident that a complication is present. As early as the first day postpartum paralysis may be noted. The degree of involvement is variable. The flexors of the foot are almost always impaired but this group is not alone involved and careful examination will frequently detect paresis in the muscles of the leg and thigh.

Paresthesias are very common and may be the first complaint upon recovering from the anesthesia. "Numbness," "dead feeling," "pins and needles," "my foot is asleep," are complaints which often precede leg pain.

Rarely slight edema of the ankle, as well as the more frequent cold and mottled skin, a vasomotor result, are present. The sensory examination may disclose findings ranging from the normal to an entire loss of sensation. The ankle jerk is commonly absent but may be increased. The knee jerk may also show abnormalities.

As time elapses atrophy of muscle proceeds and in a short time may be marked. The sciatic nerve may be exquisitely tender along its course.

At this point it may be interesting to note that cows are subject to the same lesion and that Romberg, who was familiar with this lesion in 1851, quoted Gelle in 1826 as describing 11 cases of paraplegia in cows after calving. Felming in 1896 found negative evidence of injury in the spinal canal. In two of our cases a spinal tap was entirely negative and the spinal fluid did not contain red cells.

Recovery depends upon the extent of injury but this is difficult to determine immediately postpartum.

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four hours, and the patient exhausted. There was thirty hours dry labor. The baby weighed 8 pounds 2½ ounces. It was noted that there was a very tight fit between the head and the pelvis. Good application was obtained. The patient had a low-grade fever for five days postpartum. On the tenth day pain was present in the left thigh and the next day the patient was unable to swing her legs out of bed as the left leg was very stiff and painful. Phlebitis was ruled out. Three months after delivery the patient was gaining in activity and the pain in the extremities was almost gone.

CASE 2.—(267331) V. H., aged twenty-three, black, gravida ii, para ii. The past history was negative. A previous pregnancy resulted in a live baby weighing 7 pounds 4 ounces; normal spontaneous delivery, R.O.A.; duration of labor, thirty-six hours. The antepartum period of the present pregnancy was negative. The delivery was extremely difficult and midforceps were used. After a labor of thirty-eight hours after several attempts to rotate to L.O.P. position were made without result, and after Simpson forceps proved unsuccessful, Barton forceps were employed. The baby weighed 7 pounds 3 ounces. The patient stated that before delivery she had had a great deal of pain in her right thigh posteriorly and a feeling of numbness in her right leg. This pain was aggravated by uterine pains. Immediately postpartum she noticed that she could move her right foot only slightly and that it felt weak. She was examined about a week postpartum, and it was noted that she had a right foot drop. Examination fourteen days postpartum showed no change in the upper extremities but a definite right foot drop, the foot being held in equinovarus position. The right lower extremity was much weaker than the left. The flexors and extensors of the right hip showed fair strength but the abductors and adductors on the right were weak as compared with the left, the abductors being weaker than the adductors. The flexors and extensors of the right knee were also much weaker than those on the left. All the deep reflexes were hyperactive, but those on the right were less active than those on the left. No Babinski was present. The position of toe-sense was lost in the right big toe. Vibratory sensation was also lost. On the lower third of the right thigh there was occasional loss of pinprick sensation. Below this in the lower third of leg and foot, there was marked loss of temperature sense and of pain, but not of touch. This was especially so on the lateral anterior surface. The sciotar was tender in the lower third on the right. Three months later the patient still had difficulty with her right foot. Flexion at the right knee was weaker than at the left and flexion at the ankle was also weaker on the right than on the left. Some anesthesia was still present over the lower third of the lateral surface of the right leg. Four months after delivery there was no change in sensation, and no paralysis was demonstrable.

CASE 3.—(247836) M. T., aged twenty-seven, black, gravida i, para i. The past history was negative except for an attack of rheumatic fever about twenty years before. The patient had a very mild mitral insufficiency. Delivery was spontaneous. An episiotomy was done which extended into the rectum. On the first day postpartum the patient noticed for the first time that her right lower extremity was numb and dead. The upper extremities were normal. A right foot drop was present. Both knee jerks were hyperactive, more pronounced on the right. A right ankle jerk was present. The left was just elicited. Flexion and extension of the knee were slightly weakened on the right with marked weakness of the adductors and abductors on the right as compared with the left. Below the lower third of the right leg there was complete loss of sensation to touch. Neither sciatic nerve was tender. There was no tenderness anywhere in the extremity. A lumbar puncture was done and was entirely negative. No blood was noted in the spinal fluid.

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was present in the left lower extremity below the patella. The left calf was exquisitely tender and tenderness also was present along the lower third of the left thigh. No tenderness was made out at the sacroiliac joints or along the course of the sciatic nerve. Three months later the patient stated that she did not have any difficulty when walking unless she walked a great deal and then felt very tired. Neurologic examination disclosed only a more active knee jerk on the left side.

CASE 8.—(320649) R. G., aged thirty-five, black, primipara, para ii. This patient was referred to us by the Neurological Institute because of the interest we had shown in similar cases. The patient had been delivered one month previously at another hospital in New York City. The delivery was extremely difficult. Mid-forceps had been used and a dead baby delivered. Immediately upon recovery from the anesthetic the patient noticed that her left lower extremity was "numb and dead." Pain developed the next day. A vesicovaginal fistula had healed. The past history was entirely negative. Examination showed a small toddle walking with difficulty and dragging her left leg. Slight tenderness was present in the left lower quadrant and over the symphysis. The upper extremities were normal. All muscles of the left lower extremity showed marked weakness. Flexion and extension at the left hip were definitely impaired. There was no motion at the left ankle. Sensation was diminished over the lateral surface of the left leg and foot. The right knee jerk was more pronounced than the left. The left ankle jerk was absent. Stereographs of the pelvis showed some separation of the symphysis. Examination three months later showed that marked changes and considerable difficulty in walking were still present. The patient became pregnant about this time and did not show evidence of pressure during the antepartum period. Because of the previous delivery she had an elective cesarean section at term. When last seen about one year later there was still evidence of the earlier injury.

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**Smith, Morrison, and Sladden: Spontaneous Rupture of the Spleen in a Pregnant Woman, Lancet 1: 694, 1933.**

A three months pregnant patient, aged thirty-one, began having weakness and pain below the costal angle on the left anterior side, although no injury had occurred. In twenty-four hours, dullness occurred in the groins, the pulse rate increased, and a slight fever developed. At the operation, a three-fourth-inch bleeding rupture between the hilum and the splenic notch was found. A few splenic adhesions were present. The spleen was removed and after a somewhat prolonged hospital stay the patient was discharged. She delivered a normal female infant at term, although there had been some albuminuria in the last weeks.

The noteworthy features are: (1) Splenomegaly, possibly due to Banti's disease; (2) splenic rupture without trauma; (3) associated pregnancy, which continued to term, and (4) improvement in health, subsequent to splenectomy.

II. CLOSE HESSELTINE.

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which it was possible to see a mass lying between the presenting head and the urinary bladder. The presence of central placenta previa had also been confirmed clinically. Cesarean section was done with complete confirmation of the findings. Since this preliminary report, we have subjected a large number of patients with normal pregnancy to roentgenologic examinations to determine the relationship of the presenting part of the fetus to the urinary bladder. In addition, all patients who have shown abnormal bleeding of any character during the last trimester have been similarly studied, and the x-ray interpretations have been correlated with clinical and operative findings. We have thus not only been able to confirm our earlier observations, but have also gained additional knowledge regarding the accuracy of the method, the difficulties which may be encountered in the differential diagnosis, and the advantages of following a definite technical procedure.

#### ROENTGENOLOGIC TECHNIC

The radiographic procedure should be carried out on a table equipped with a Potter-Bucky diaphragm, and under circumstances permitting rapid exposure. A catheter is inserted into the urinary bladder, the bladder is emptied, and about 40 cc. of a 12½ per cent solution of sodium iodide or other contrast material is instilled. The catheter is then withdrawn. We stress two details in this procedure: first, the amount of the instilled solution should only be sufficient to outline the urinary bladder. It should not be sufficient to distend it completely as in this way enough pressure may be exerted against the uterus to produce difficulties in the analysis of the findings. We feel that this factor of overdistention gave us most of our difficulties in our earlier cases, and in several instances led to erroneous conclusions. The only call for instilling a contrast material is to demarcate the margin of the bladder, and any filling which exceeds this would be of no additional value, and might distort the findings. Second, the catheter should be withdrawn before making the roentgenogram. If it is left in the bladder, it may distort its margin to such an extent that the study may have to be considered unsatisfactory. Attempts to use air to distend the bladder instead of a contrast solution were made in some of our cases (Fig. 4), but we feel this is less satisfactory than the method which we advocate, although under careful control it may yield the same information. Our first case which we have previously reported<sup>2</sup> demonstrated conclusive findings without contrast material in the bladder, but with the bladder clearly outlined on the film.

The usual anteroposterior film of the abdomen is made immediately after withdrawal of the catheter. The tube is centered over the mid or lower abdomen just as is customary for study of the fetus in normal cases. We do not angle downward into the lesser pelvis because in doing so we would probably fail to clearly demonstrate the soft-tissue space between the urinary bladder and the head of the fetus (see Fig. 1). We prefer to use a large enough film to show the entire fetus, as other valuable information may be revealed from a study of the fetal structure or from the soft tissue shadows, such as the placenta, in the upper portion of the uterus. Exposure time should be the shortest consistent with the available equipment, in order to reveal a maximum amount of detail without distortion from motion of the fetus.

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We feel that a lateral film is of very little value to demonstrate placenta previa. It may, however, be of considerable indirect help if one can establish thereby the

roentgenogram the fold of peritoneum may be demonstrated as a narrow line of increased translucency. In the third trimester of pregnancy, the lower uterine segment is a comparatively thin-walled, muscular tube, also measuring only a few millimeters in diameter. The total diameter of the soft tissues normally lying between the inner wall of the gravid uterus and the lumen of the bladder scarcely exceeds one centimeter, and on the roentgenogram this space normally appears to be only about 6 to 8 mm. in depth. If then we can demarcate the inner wall of the lower uterine segment, we should be able to demonstrate any abnormal increase in the width of this area. For this factor, the presence of the fetal head in the lower uterine segment is an excellent landmark. Covered only by a very thin layer of soft tissue, the bones of the head give a very accurate demarcation of the inner wall of the uterus. We have demonstrated this repeatedly in control cases of normal pregnancies. We have found that the presenting head invariably lies directly against the lower anterior wall of the uterus unless it is displaced upward by a solid mass, either by the placenta, blood clots from a premature separation of the placenta, or from some abnormality of the fetus or pelvis. Furthermore, this portion of the uterus produces a crescentic pressure deformity of the upper posterior surface of the urinary bladder. It is on a careful analysis of the densities between the bladder margin and the skull of the fetus that we depend for the roentgenologic diagnosis of placenta previa. If a breech or transverse position is encountered, these findings probably cannot be established, as in the absence of the head of the fetus from the lower uterine segment, the inner wall of the uterus cannot be accurately determined. It is, therefore, apparent that this study depends on the presentation of the head of the fetus. We have studied one case (Fig. 11) of placenta previa with the fetus in transverse position in which we were unable to make the diagnosis roentgenologically.

The normal placenta varies from 2 to 3 cm. in thickness. In low implantations the placenta has a tendency to be relatively thinner than normal, since it spreads out over a larger area because of the limited blood supply of the lower uterine segment. The shape of the placenta conforms to that of the uterine wall externally, and to the pressure from the fetus and the amniotic fluid internally. Its outer margin is therefore convex, and its inner margin concave. The concavity of the inner margin is especially evident when the rounded head of the fetus rests directly against it in the lower uterine segment. The demonstration of a mass of these characteristics interposed between the fetal head and the urinary bladder constitutes the diagnostic picture.

The size and position of the presenting mass may allow one to express an opinion whether the implantation is central or partial in type.

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The size and position of the presenting mass may allow one to express an opinion whether the implantation is central or partial in type.

In these the bleeding was demonstrated at delivery to have been caused by premature separation of the placenta. An analysis of nine representative cases is made herewith. We have also studied a group of normal patients, but wish again to call attention to the many cases which have now been demonstrated by intravenous urography in which the normal picture has been clearly established. Figs. 3 and 4 show the typical findings in uncomplicated pregnancies.

The following cases illustrate the roentgenologic findings, and are representative of the various conditions which we have encountered in our studies.

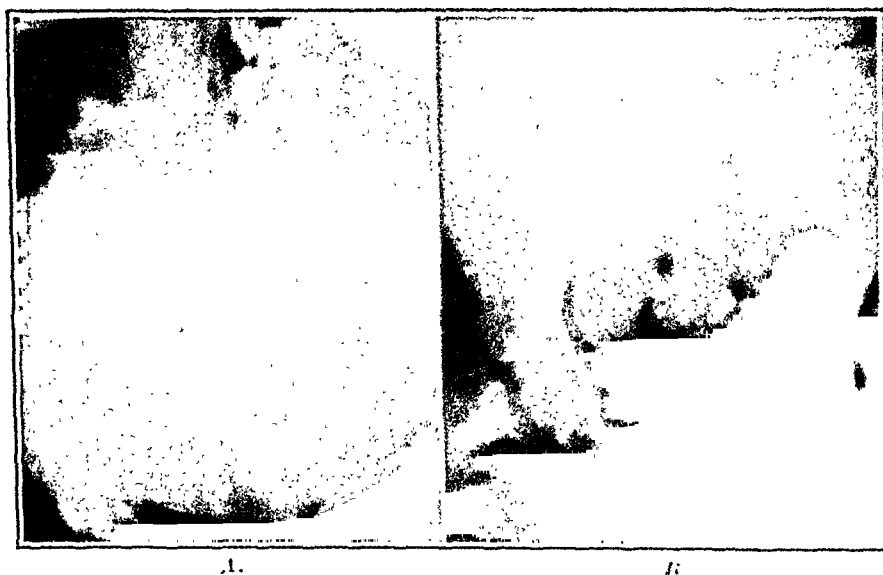


Fig. 4.—Pneumocystograms of two normal pregnancies. A, Breech presentation; note that any abnormal soft tissue mass could probably not be identified. B, Bladder slightly but sufficiently distended with air to show normal soft tissue space between the head and the bladder margin.

#### REPORT OF CASES

CASE 1.—(Fig. 5.) Mrs. R. T., aged twenty nine, gravida i, para 0. Last menstrual period occurred Jan. 20, 1933. Pregnancy proceeded normally until Oct. 27, 1933, when she developed cramplike pains. The membranes ruptured spontaneously and were followed by profuse bleeding. Abdominal examination showed fetus at term in occiput right anterior position. The fetal heart was of good quality. Rectal examination showed the head below the spines. The cervix was partially effaced, and dilated to a diameter of about 3 cm. There were no palpable masses in the lower uterine segment. Roentgenologic examination with cystogram (Fig. 5) revealed the fetal head low in the pelvis, producing typical pressure defect in the upper portion of the urinary bladder, with no evidence of placental mass in the lower uterine segment. The possibility of placenta previa was thus eliminated by the roentgenologic and rectal findings, permitting a clinical diagnosis of premature separation of the placenta. A No. 4 Voorhees' bag was inserted, preceded by digital examination through the cervix which failed to reach the placenta. Upon expulsion of the bag, the bleeding became severe. At this time rectal examination showed complete dilatation of the cervix with the head on the pelvic floor. Low forceps were

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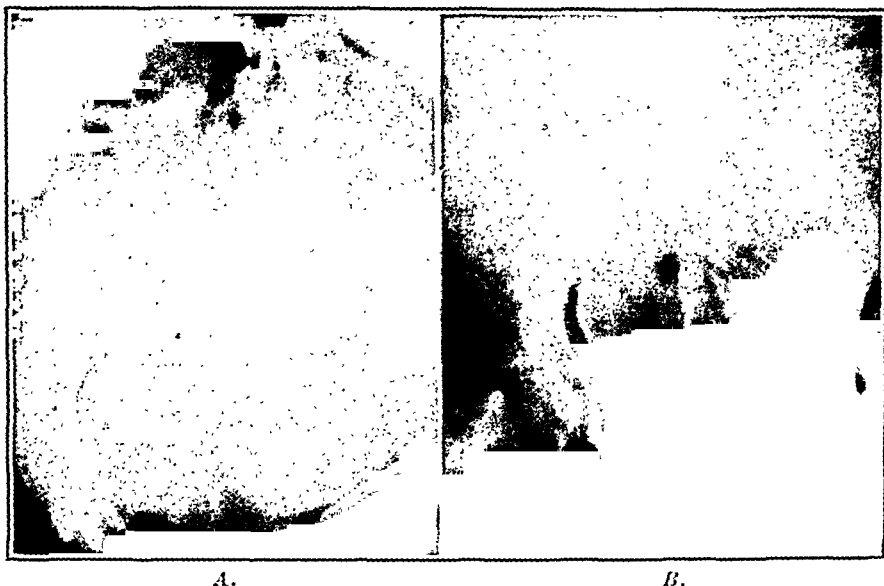


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the left. At expulsion of the bag spontaneous delivery of a living premature infant occurred. Study of the placenta showed apparently complete separation of its circumference had separated prematurely for a distance of from 1 to 2 cm. This established the final diagnosis of low implantation with premature separation of the placenta.

CASE 3.—(Fig. 6, B.) Mrs. P. V., aged twenty-two, para 4, gravida vi. The last menstrual period took place Dec. 12, 1932. Pregnancy progressed normally until Sept. 19, 1933, when she had a sudden gush of blood from the vagina followed by labor pains. At the time of admission there was no active bleeding. Examination of the abdomen showed the fetus at term in O.L.A. position. The fetal heart tones were normal. Uterine contractions were taking place every three to five minutes and persisted for thirty to fifty seconds. Rectal examination showed the head of the fetus at the spine, the cervix almost completely effaced, and dilated about 2 cm. There were no palpable masses in the lower uterine segment. A cystogram (Fig. 6, B) revealed the fetal head low in the lesser pelvis, definitely engaged, with no evidence of the placenta in the lower uterine segment. The possibility of placenta previa was thus eliminated, indicating that the bleeding was probably due to previa.

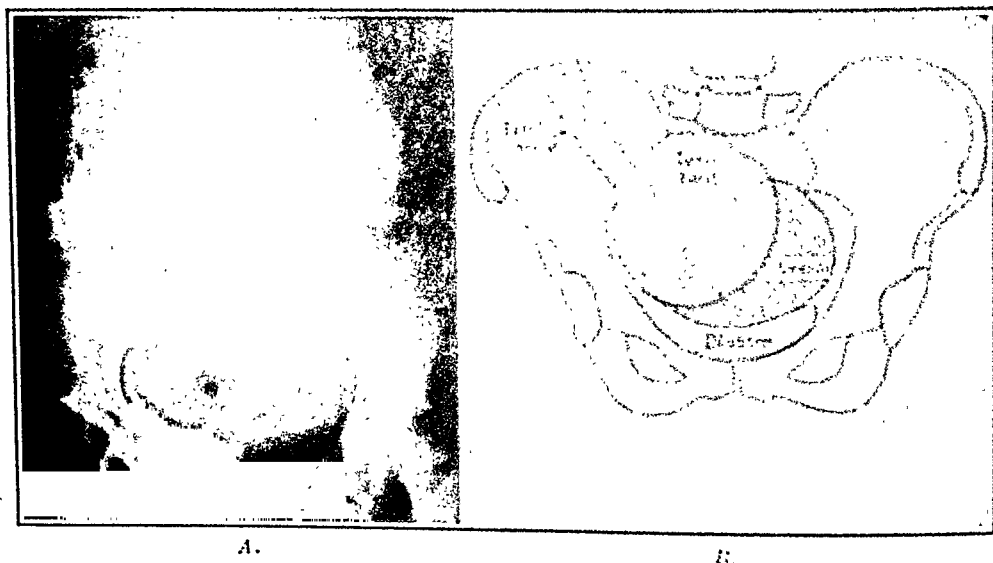


Fig. 7.—A, Roentgenogram of single pregnancy showing a soft tissue mass separating the fetal head from the upper margin of the urinary bladder. B, Diagram of roentgenologic findings, showing the implantation of the placenta in the lower uterine segment. (Published in *Am. J. Roentgenol.*)

ture separation of the placenta. Labor progressed normally. A living baby was delivered spontaneously. Examination of the placenta showed a large area of premature separation of what appeared to be a normally implanted placenta.

CASE 4.—(Fig. 8.) Mrs. V. T., aged twenty, para 0, gravida i. The last menstrual period occurred May 22, 1932. Pregnancy progressed normally until Jan. 6, 1933, at which time she had a sudden hemorrhage associated with a dull heavy pain in both lower quadrants. On admission she was bleeding moderately. Examination showed pregnancy to be near term, with the fetus in O.L.P. position. The head was high over the pelvic inlet. The fetal heart was of good quality. Rectal examination showed a long firm cervix. There was a soft boggy mass on the left extending over the internal os. The fetal head could be palpated on the right, lateral to the cervix, but it could not be impressed into the pelvis. The clinical diagnosis was central placenta previa. A cystogram (Fig. 8) revealed the fetal head overlying the lesser pelvis, but separated from the upper surface of the urinary bladder by a

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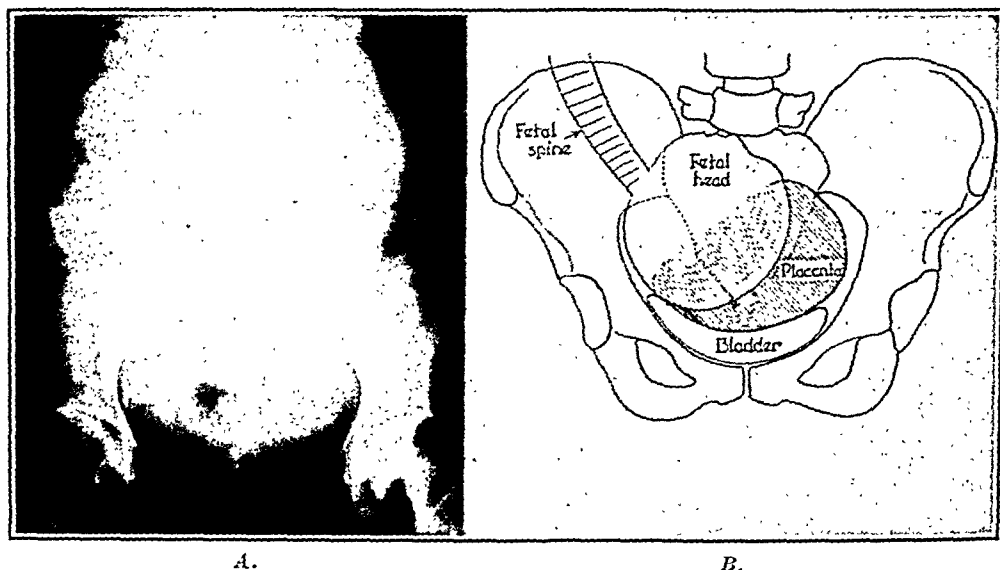


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CASE 6.—(Fig. 10.) Mrs. L. B., aged forty, para ii, gravida iv. The last menstrual period began Feb. 19, 1932. Pregnancy progressed normally until September, 1932, when she began to notice occasional spotting from the vagina. This occurred intermittently and was never profuse until October when she bled moderately and passed clots of blood. This continued for one day. On November 15 she had a sudden severe hemorrhage which brought her to the hospital. Until this time she had not received prenatal care of any kind. Upon admission to the hospital she

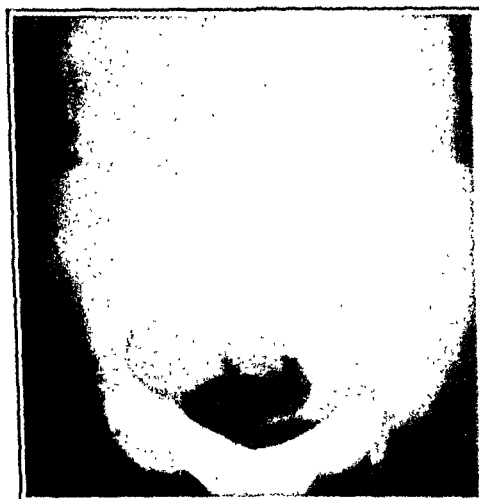


Fig. 10.

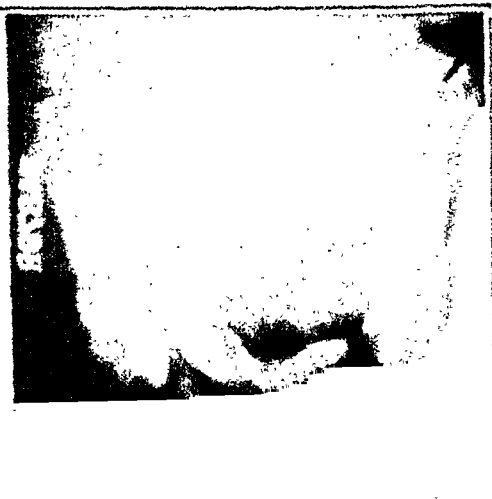


Fig. 11

Fig. 10.—Case 6. Cystogram of pregnancy in third trimester showing widened space between bladder and fetal head. Diagnosis of central placenta previa was confirmed clinically and by cesarean section.

Fig. 11.—Case 7. Cystogram of pregnancy showing transverse position of fetus. No conclusions were drawn as to position of placenta. A clinical diagnosis of placenta previa centralis was confirmed by cesarean section.

was bleeding moderately, and appeared to have lost a large amount of blood. Abdominal examination showed pregnancy at term with the fetus in O.L.T. position. The fetal heart was normal. Rectal examination showed the head high overlying the pelvic inlet. The cervix admitted one finger, permitting palpation of a large boggy mass through which the fetal head could not be reached. A cystogram (Fig. 10) revealed a fairly wide separation between the fetal head and the upper margin of the urinary bladder, with evidence of a soft tissue mass producing this separation. These roentgenologic findings indicated a low implantation of the placenta, probably placenta previa centralis. Cesarean section was done, with delivery of a living baby. The placenta was attached to the anterior wall of the lower uterine segment and completely covered the internal os.

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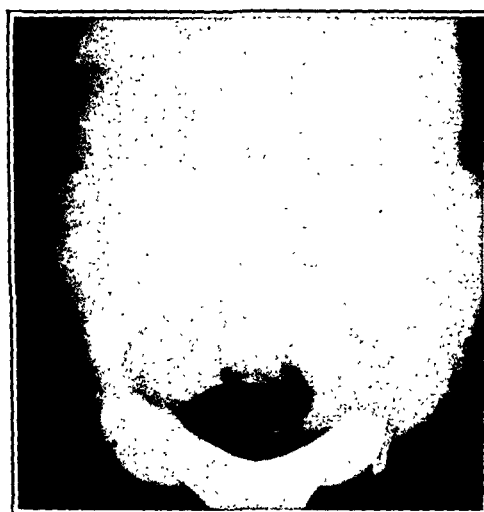


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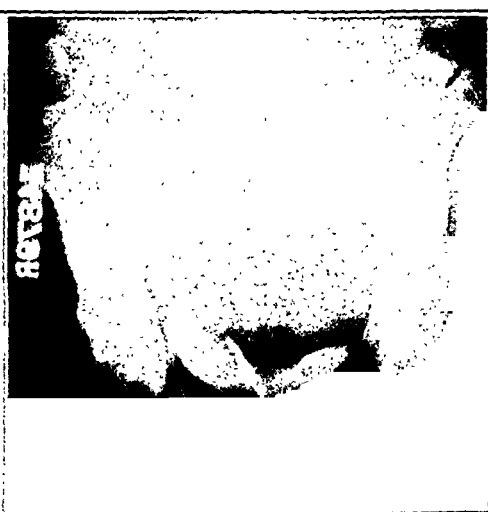


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CASE 9.—(Fig. 14.) Mrs. H. K., aged forty, para 3, gravida 4. Last menstrual period occurred June 8, 1933. Pregnancy progressed normally until Feb. 19, 1934, when she began to bleed from the vagina. This bleeding was not associated with pain or backache. Examination revealed an eight-month pregnancy in O.U.A. position. Rectal examination showed the head high over the pelvic inlet. The presenting part could not be impressed into the inlet. The cervix was not dilated. There was a soft, pulsating mass to the left and posterior to the cervix, apparently lateral in position, without overlying the internal os. A cystogram (Fig. 14) revealed a fusiform mass separating the fetal head from the upper margin of the urinary bladder, but more prominent in the left lateral portion of the lower pelvis, with the fetal head deviated to the right. A roentgenologic interpretation of low implantation, probably of the partial placenta previa type, was made. Cesarean section was planned as close to term as possible. On March 18, 1934, the patient began to bleed, and developed severe labor pains. The cervix dilated rapidly, and, within a few minutes, a stillborn fetus was delivered. Fetal death had been indicated by failure to hear the fetal heart at the onset of severe pain. Inspection of the



Fig. 14.—Case 9. Cystogram of pregnancy with abnormal bleeding. Mass is demonstrated to separate the head of the fetus from the left lateral half of the upper margin of the bladder. Partial placenta previa was confirmed by delivery and inspection of placenta.

placenta showed the membranes ruptured at its margin, with a tongue-like process of placenta covered with old blood clots. The case was therefore one of partial placenta previa.

#### SUMMARY

A complete report of our experience with our roentgenologic method of diagnosis of placenta previa is presented herewith. We have now applied this type of study in 35 cases with abnormal uterine bleeding during the third trimester of pregnancy. Careful clinical observations were made, so that an accurate correlation between clinical and roentgenologic findings could be established. A routine technic has been found desirable, and we are giving the details of the procedure since we consider them essential to avoid possible errors in interpretation. The anatomic relations and roentgenologic findings on which we base our conclusions are presented, and these are illustrated by case reports and numerous figures.

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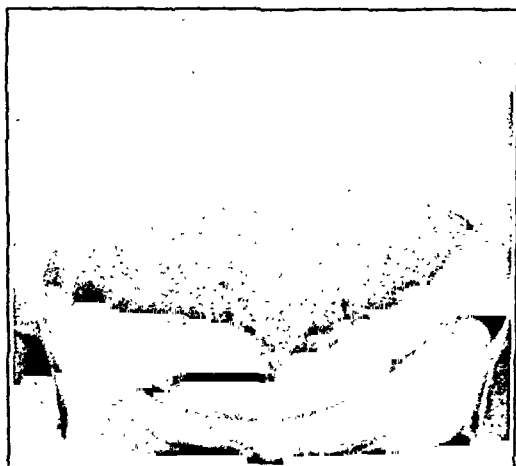


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## THE PRODUCTION OF AN ACTIVE ENDOMETRIUM IN THE HUMAN CASTRATE

THEODORE NEUSTAEDTER, M.D., LL.M. (DUBLIN), F.A.C.S.,  
NEW YORK, N. Y.

**F**OLLOWING the standardization of the female sex hormone by Allen and Doisy,<sup>1</sup> the isolation of the active principle of the corpus luteum (progesterin) by Corner and Allen,<sup>2</sup> and the artificial production of the cyclical changes in the laboratory animals by the use of these agents, their application to the human mechanism has been attempted. Since their clinical value is still questionable, their universal use as therapeutic remedies lies in the future.

Werner and Collier<sup>3</sup> have reported that they were able, by the daily injection of 200 Allen-Doisy rat units of theelin into castrated women for a period of two weeks, to promote marked endometrial growth and uterine bleeding during and at the end of the experiment. Kaufmann,<sup>4</sup> using 10,000 mouse units of progynon benzoate (female sex hormone in combination with a benzoate radical) for twenty-one days, followed by seven daily injections of 5 rabbit units of luteal serum (estrin-free progesterin), succeeded in producing a premenstrual endometrium in the human castrate for the first time. Carl Claiberg<sup>5</sup> achieved the same results independently of Kaufmann, but published his work at a later date.

This indisputable evidence at least insures us progress in the proper direction. To the previously published data I can now offer further experimental evidence of the biological activity of an ovarian extract given by mouth.

G. V. Smith and O. W. Smith<sup>6</sup> have prescribed estrin in this form (progynon tablets) to patients whose urine previous to the oral administration showed no estrin excretion, and demonstrated its presence in the urine after its ingestion. They believe that such findings offer conclusive evidence that estrin supplied in this form is absorbed when orally administered.

*Case Report.*—F. L., white female, aged twenty-eight was admitted to the Gynecological Division of the Central Neurological Hospital on Sept. 12, 1932.

*Chief Complaint:* Pain over the right half of back referred to the central portion of the lower abdomen; amenorrhea, hot flashes, cardiac palpitation, occasional fainting spells, insomnia and excessive perspiration. The patient lost 26 pounds in the previous year.

*Family History:* Father died of "bladder trouble." Married twice; four children by her first husband; two died at birth and two at three months. No children with her second husband.

\*Read before the Section of Obstetrics and Gynecology, New York Academy of Medicine, May 22, 1934.

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Bimanual examination showed external genitalia hypoplastic. Peritoneum firm, no cystocele or rectocele. Vaginal fornices were shallow. The uterus was small, anterior and pointed slightly toward the left; it was not freely movable. The adnexa were not palpable. The cervix was small, atrophic, and pale.

Laboratory findings in general, negative.

After entering the hospital, the patient complained of occasional slight vaginal spotting, so that a diagnostic curettage was indicated. There was no evidence of frank bleeding and cervical dilatation was accomplished with considerable difficulty. The length of the uterine cavity from external os to fundus was 2½ inches. A small amount of tissue was removed. The uterine cavity felt atrophic and smooth.

*Pathologic Report* (Dr. Vera Dolgopul).—The specimen consisted of minute, soft, red and gray particles of tissue. The sections showed two fragments of cervical



Fig. 2.—Curettings after oral administration of additional 56,400 R. U. of estrin, followed by administration of progestin: Pale columnar epithelium; glands in loose stroma. (Magnification, Leitz periplane eyepiece 16, objective 3.)

mucosa, and a few blood clots. The endometrium was represented in two or three places by short rows of low cuboidal epithelium (without underlying stroma), which were enclosed in the blood clots. There was no evidence of gland formation.

*Diagnosis:* Atrophic endometrial epithelium (Fig. 1, A).

On Feb. 5, 1933, oral administration of progynon was begun. For a period of twenty days the patient received progynon tablets (45 R.U.) three times daily. This was followed by progynon tablets (600 R.U.) two, three times daily for a period of fifteen days. The total amount given for the thirty-five days was 56,700 R.U. of the female sex hormone, after which the hot flashes disappeared, the nervous palpitation diminished practically to a minimum, the patient was able to sleep throughout the night and the attacks of excessive perspiration disappeared. The patient also described a sensation of breast fullness. On the seventeenth day there was slight spotting. On the thirty-sixth day a second curettage was performed. The cervix was softer than on the previous occasion. The color was pinkish, its

Bimanual examination showed external genitals hypoplastic. Perineum firm, no cystocele or rectocele. Vaginal fornices were shallow. The uterus was small, anterior and pointed slightly toward the left; it was not freely movable. The adnexa were not palpable. The cervix was small, atrophic, and pale.

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After entering the hospital, the patient complained of occasional slight vaginal spotting, so that a diagnostic curettage was indicated. There was no evidence of frank bleeding and cervical dilatation was accomplished with considerable difficulty. The length of the uterine cavity from external os to fundus was  $2\frac{1}{2}$  inches. A small amount of tissue was removed. The uterine cavity felt atrophic and smooth.

*Pathologic Report* (Dr. Vera Dolgopol).—The specimen consisted of minute, soft, red and gray particles of tissue. The sections showed two fragments of cervical



Fig. 2.—Curettings after oral administration of additional 86,400 R. U. of estrin, followed by administration of progestin: Pale columnar epithelium; glands in loose stroma. (Magnification, Leitz periplane eyepiece 16, objective 3.)

mucosa, and a few blood clots. The endometrium was represented in two or three places by short rows of low cuboidal epithelium (without underlying stroma), which were enclosed in the blood clots. There was no evidence of gland formation.

*Diagnosis:* Atrophic endometrial epithelium (Fig. 1, A).

On Feb. 5, 1933, oral administration of progynon was begun. For a period of twenty days the patient received progynon tablets (45 R.U.) three times daily. This was followed by progynon tablets (600 R.U.) two, three times daily for a period of fifteen days. The total amount given for the thirty-five days was 56,700 R.U. of the female sex hormone, after which the hot flashes disappeared, the nervous palpitation diminished practically to a minimum, the patient was able to sleep throughout the night and the attacks of excessive perspiration disappeared. The patient also described a sensation of breast fullness. On the seventeenth day there was slight spotting. On the thirty-sixth day a second curettage was performed. The cervix was softer than on the previous occasion. The color was pinkish, its

two, three times daily. There was a slight staining, and days after treatment was resumed. Immediately following the cessation of treatment small doses of progestin in the form of luteodiotin were administered intramuscularly. An aqueous solution containing 10 rabbit units of an assayed extract of the active principle of the corpus luteum (progestin), was dissolved in 10 cc. of sterile olive oil. Two daily intramuscular injections of this combination were given; 1.5 cc. for the first five days and 2.5 cc. on the sixth day. Two days following the last injection the patient was curetted for the third time. The cervix was dilated without difficulty, the distance from the external os to fundus was still about three inches, and the cervix was red and a normal reddish color.

*Report.*—The specimen consisted of clots of mucus and small blood clots. Macroscopically several pieces of the endometrium showed deep invagination of the epithelium, with formation of slightly tortuous glands which secreted mucus. The endometrial stroma in places was loose and edematous, and contained enlarged capillaries. In several areas the stroma showed hemorrhagic infiltration.

*Diagnosis:* Endometrium of a late interval phase. Hemorrhagic infiltration of the stroma (Figs. 2, 3, and 4).

#### COMMENT

It seems that within two and one-half years following human castration, atrophy of the endometrium as well as of the remaining structures of the uterus and cervix occurs. This is well exemplified by the pelvic examination and the findings following the first curettage. According to Schroeder<sup>7</sup> a basal layer must exist in order to provide for the regeneration of an active endometrium. Repeated curettings in women over a number of years produce complete cessation of menstruation; i.e., failure of the endometrium to regenerate due to complete removal of the basal layer following excessively deep curettage.

The purpose of this experiment was to determine whether or not an extract of female sex hormone by oral administration was capable of inducing an active endometrium. The dosage was not exactly calculated, as Werner and Collier<sup>8</sup> have done with injections of theelin. It does not seem possible to estimate definitely even an approximate dosage necessary to produce the desired result in each individual. In this instance a large dose, approximating 56,700 R.U. of estrin, was administered orally over a period of thirty-five days. This was purely arbitrary, so that if the expected result was not obtained the futility of a larger dose would be apparent. As evidenced by the report on the second curettings a beginning interval phase was produced. At the same time, the entire symptom complex, which was the terminal effect of the castration, was reduced to a minimum. In addition, definite activity was experienced in the breast and sexual inclinations returned. There is no doubt that a smaller dosage would have alleviated the menopausal syndrome, but it is questionable whether or not an active endometrium could have been produced.

To determine further whether small doses of progestin would change the interval phase to that of progestational activity, 10 rabbit units of an estrin-free progestin were injected over a period of six days,

two, three times daily. There was a slight staining four days after treatment was resumed. Immediately following the cessation of treatment small doses of progestin in the form of luteohormon were administered intramuscularly. An ampoule, containing 10 rabbit units of an assayed extract of the active principle of the corpus luteum (progestin), was dissolved in 10 c.c. of sterile olive oil. Six daily intramuscular injections of this combination were given; 1.5 c.c. for the first five days and 2.5 c.c. on the sixth day. Two days following the last injection the patient was curetted for the third time. The cervix was dilated without difficulty, the distance from the external os to fundus was still about three inches, and the cervix assumed a normal reddish color.

*Report.*—The specimen consisted of shreds of mucosa and small blood clots. Microscopically several pieces of the endometrium showed deep invagination of the epithelium, with formation of slightly tortuous glands which secreted mucus. The endometrial stroma in places was loose and edematous, and contained engorged capillaries. In several areas the stroma showed hemorrhagic infiltration.

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# LOW CALCIUM TETANY OF THE NEWBORN AS A PROBLEM FOR THE OBSTETRICIAN

ALFRED M. HELLMAN, B.A., M.D., F.A.C.S., AND  
JACOB L. ROTHSTEIN, B.A., M.D., New York, N. Y.

IT IS the purpose of this paper to bring to the attention of the obstetrician the problem of tetany in newborn infants, so that he may become acquainted with the symptom-complex presented, the method necessary for the early recognition of the syndrome and the therapeutic procedures at his disposal.

Until recently, the existence of tetany during early life was almost universally denied. The pediatric textbooks are replete with such statements. Von Berg,<sup>1</sup> Pearce,<sup>2</sup> Holt and Howland,<sup>3</sup> Lucas<sup>4</sup> and Peet<sup>5</sup> all set the lower limit for the appearance of tetany at three months of age. Moros characterizes the first two weeks of life as "a time at which tetany never occurs." Gruber and Bonart state that "whether or not such a condition (tetany) may be found in the first weeks of life is doubtful." As recently as 1929, Hess<sup>6</sup> declared that "authentic tetany of the newborn has not been described."

During the last three years, reports of cases of tetany with a lowered calcium concentration in the blood, occurring in newborn infants within the first three weeks of life, have appeared in the pediatric literature with increasing frequency. Proved cases have been described by Shannon,<sup>7</sup> Bass and Karelitz,<sup>8</sup> Nesbitt-Mason,<sup>9</sup> Small,<sup>10</sup> Guild,<sup>11</sup> Blossom and Nicholas,<sup>12</sup> Gaberman,<sup>13</sup> Craig,<sup>14</sup> Simcock,<sup>15</sup> and Rothstein,<sup>16, 20</sup>

During the past fifteen months, we have observed two proved cases of low calcium tetany in the newborn and one probable, though unproved, case. The two proved cases have been reported by one of us (J. L. R.) in detail in the pediatric literature.<sup>16, 20</sup>

The first case was that of a full-term 4-pound 4-ounce male infant, delivered from a preeclamptic mother without the use of instruments at the Sydenham Hospital. During the first two weeks an unexplained hyperpyrexia was present followed by the development of muscular twitching on the thirteenth day and by the appearance of laryngeal and carpopedal spasms on the seventeenth and eighteenth days. The blood calcium content was 7.4 mg. The symptoms subsided after intensive calcium gluconate therapy given intravenously, intramuscularly, and orally. Viosterol also was given.

The second patient was a 6 pound 12 ounce, full-term male infant, delivered by low forceps at the Lenox Hill Hospital. Symptoms and signs of an aspiration pneumonia were observed several hours after birth which cleared after three days of hyperpyrexia. Twitching of the muscles of the face and extremities appeared on the seventh day, followed by a convulsion the next day. The blood calcium content was 7.5 mg. A prompt cessation of symptoms occurred after repeated intravenous and intramuscular administration of calcium gluconate. The blood calcium concentration, however, did not rise until fourteen daily intravenous injections

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two instances (Shannon's third case; Nephel's first case).<sup>10</sup> Rothstein<sup>11</sup> has recently observed his third proved case of tetany of the newborn occurring in a thirty-six-hour old, seven and a half months' premature infant with a complicated fever and edema, but without twitching or convulsions. The edema was primarily in character and localized to the pubic area, the vulva and the lateral aspects of both thighs. The blood calcium content was 7.0 mg. The edema gradually disappeared after daily intravenous administration of calcium gluconate and the blood calcium finally rose to 9.3 on the twelfth day of therapy.

#### DIAGNOSIS

Thus the symptom-complex presented may consist of one or more of the following symptoms and signs: hyperpyrexia, vomiting, twitching of the muscles of the face or of the extremities, convulsions, a positive Chvostek phenomenon, laryngospasm, carpopedal spasm and subcutaneous edema.

Laryngospasm or carpopedal spasm, if present, is highly suggestive of an underlying tetany. However, these symptoms are not necessary for the diagnosis and their absence does not mitigate against the presence of an active tetany. In Rothstein's<sup>11</sup> second case and in Chang's<sup>12</sup> case, neither of these symptoms was noted even at the height of the convulsions when the blood calcium concentration was low.

A positive Chvostek phenomenon, although an important finding in the older, infantile type of tetany, is of very little significance in the newborn. The Chvostek sign may be negative and still a definite tetany may be present, as occurred in Small's case<sup>13</sup> with a blood calcium concentration of 5.6 mg. Furthermore, a positive Chvostek phenomenon is frequently encountered in healthy newborn infants with normal blood calcium values, as has been pointed out by Stevenson, Mitchell and Koch.<sup>22</sup>

Muscular twitching and convulsions are usually the earliest, and the most frequently encountered, symptoms to lead one to suspect the presence of tetany in the newborn. In all of the previously published cases of active tetany, twitching or convulsions have been present at some time or other in the course of symptoms. However, in Rothstein's recently observed third case referred to above,<sup>11</sup> neither convulsions nor twitchings were observed and the sole clue to the diagnosis was the presence of the peculiarly localized edema.

Proof of the presence of tetany depends upon the demonstration of either a positive Erb's sign or a lowered blood calcium concentration. Although Erb's sign (the change in the quantitative reaction of the nerves to the galvanic current) is considered the most reliable index of tetany in older infants, electrical reactions in the newborn are generally too difficult to determine with any degree of certainty to make this sign of much diagnostic value. Consequently, we must rely on finding a lowered calcium concentration in the serum in order to prove the presence of tetany in a newborn infant. The normal calcium values in newborn infants have been demonstrated by Howland and Marriott<sup>23</sup> to vary between 10 and 11 mg.

#### DIFFERENTIAL DIAGNOSIS

The differential diagnosis will rest between tetany and (1) other causes for convulsions in the newborn, such as cerebral hemorrhage, intracranial injuries, edema of the brain, intrauterine meningitis, fracture of the skull with depression of a fragment causing cerebral com-

two instances (Shannon's third case,<sup>9</sup> Nesbit's first case<sup>11</sup>). Rothstein<sup>21</sup> has recently observed his third proved case of tetany of the newborn occurring in a thirty-six-hour old, seven and a half months' premature infant with unexplained fever and edema, but without twitching or convulsions. The edema was brawny in character and localized to the pubic area, the vulva and the lateral aspects of both thighs. The blood calcium content was 7.0 mg. The edema gradually disappeared under daily intravenous administration of calcium gluconate and the blood calcium finally rose to 9.3 on the twelfth day of therapy.

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The differential diagnosis will rest between tetany and (1) other causes for convulsions in the newborn, such as cerebral hemorrhage, intracranial injuries, edema of the brain, intrauterine meningitis, fracture of the skull with depression of a fragment causing cerebral com-



responsible for the baby at the onset of symptoms. It is of the utmost importance that he should be familiar with the symptom-complex, the procedure necessary to establish the diagnosis and the therapy to be employed. Whenever he is confronted by twitching or convulsions of unexplained etiology in a newborn infant, whether or not they are accompanied by such suggestive symptoms as laryngospasm or carpopedal spasm, the blood calcium content should be determined. It seems quite probable that some of the cases with convulsions which have ended fatally and were regarded as instances of "cerebral hemorrhage" or of "intracranial injury," may actually have been unsuspected instances of tetany.

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44 EAST SEVENTY-EIGHTH STREET  
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Messer A. I.: Undulant Fever and Contagious Abortion in Northumberland, Brit. M. J. 2: 856, 1934.

The author reports the results obtained by examining the serums of 425 patients for agglutinins to *Br. Abortus*. In sixteen patients (3.7 per cent) a diagnosis of undulant fever was made on serologic and clinical grounds, the serum titers varying from 1 in 125 to 1 in 3,000. The author believes this agglutination reaction to have the same value and limitations as the Widal reaction in enteric infection.

The author describes two clinical types of cases, the mild and the more severe, and appends several case histories to illustrate the different courses of the disease.

Various epidemiologic factors are discussed, with special attention to consumption of infected milk.

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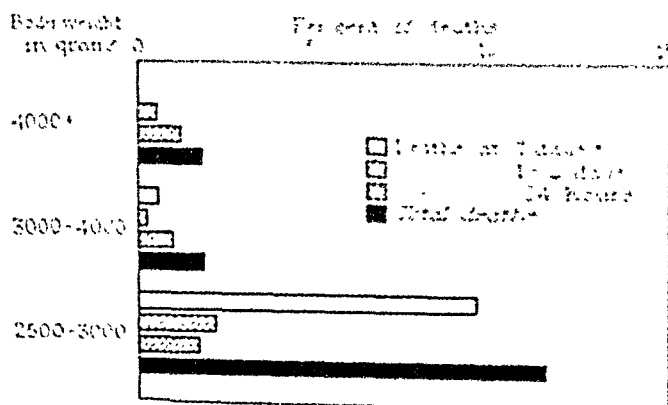
The clinical diagnoses of this group were as shown in Table I.

TABLE I

	STILLBORN	UNDER 24 HOURS	24 HOURS	7 DAYS	TOTAL
Total	21	51	19	86	187
Asphyxia and birth trauma	21	11	4	1	37
Prematurity		10	12	18	40
Prematurity, birth trauma and asphyxia		4	1	1	6
Prematurity and infectious disease		5	17	17	39
Infectious disease		11	4	20	35
Malnutrition			1	2	3

Autopsies were made in approximately half of these. In the present study, postmortem findings have not been made a basis of study in itself, but rather the age of the infant when death occurred. Using only autopsy diagnoses and cases would have left an incomplete series, and therefore all the cases have been used in determining the incidence

Fig. 1. Deaths of Term Infants in relation to Birth Weight.



of death under various conditions, with only such gross abnormalities eliminated as previously mentioned.

Ordinary statistics are often valueless since scientific statistical methods are not employed to eliminate the factors of error. In order to evaluate the significance of percentages obtained in quantitative studies of the material, the standard errors for the proportions have been determined and probabilities calculated, thus determining whether certain conclusions are warranted or doubtful.

#### FETAL MORTALITY IN RELATION TO BIRTH WEIGHT

The fetal mortality in relation to birth weight is shown in Fig. 1.

Using the 3,000 to 4,000 gm. group as a base for comparison of differences of the several groups, the number of times the difference would occur by chance alone in the process of sampling was determined from which the probability of it being due to chance is interpreted.

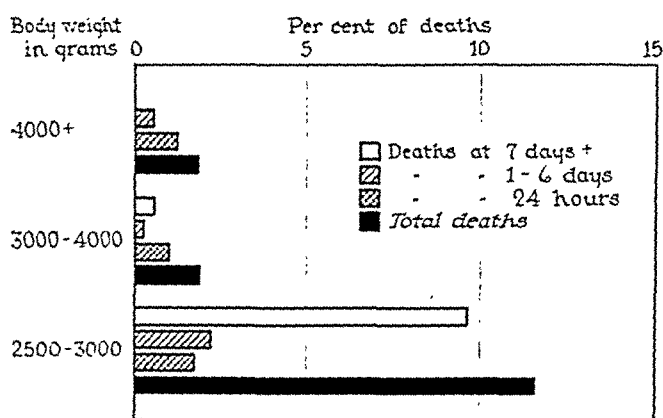
The clinical diagnoses of this group were as shown in Table I.

TABLE I

	STILLBORN	UNDER 24 HOURS	2-6 DAYS	7 DAYS	TOTAL
Total	21	31	39	89	180
Asphyxia and birth trauma	21	11	4	1	37
Prematurity		10	12	18	40
Prematurity, birth trauma and asphyxia		4	1	1	6
Prematurity and infectious disease		5	17	47	69
Infectious disease		11	4	20	25
Malnutrition			1	2	3

Autopsies were made in approximately half of these. In the present study, postmortem findings have not been made a basis of study in itself, but rather the age of the infant when death occurred. Using only autopsy diagnoses and cases would have left an incomplete series, and therefore all the cases have been used in determining the incidence

Fig. 1 Deaths of Term Babies in relation to Weight and Time of Death.



of death under various conditions, with only such gross abnormalities eliminated as previously mentioned.

Ordinary statistics are often valueless since scientific statistical methods are not employed to eliminate the factors of error. In order to evaluate the significance of percentages obtained in quantitative studies of the material, the standard errors for the proportions have been determined and probabilities calculated, thus determining whether certain conclusions are warranted or doubtful.

#### FETAL MORTALITY IN RELATION TO BIRTH WEIGHT

The fetal mortality in relation to birth weight is shown in Fig. 1.

Using the 3,000 to 4,000 gm. group as a base for comparison of differences of the several groups, the number of times the difference would occur by chance alone in the process of sampling was determined from which the probability of it being due to chance is interpreted.

est mortality rate, being lower than that of either the very short or the very long labors. When applying statistical formulae and probability determinations, no real difference can be demonstrated in successive groups except for the very long labors. Therefore, some of the extremes may be tested for significant differences. A short-cut method of inspection may be employed in selecting groups of possible significant difference by means of the following principle. If, for two

Fig 2 Fetal Mortality in relation to Duration of Labor  
Induced Deliveries

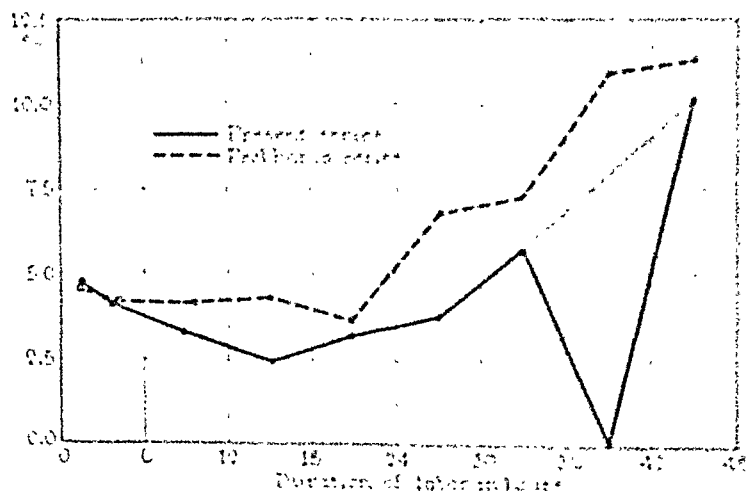
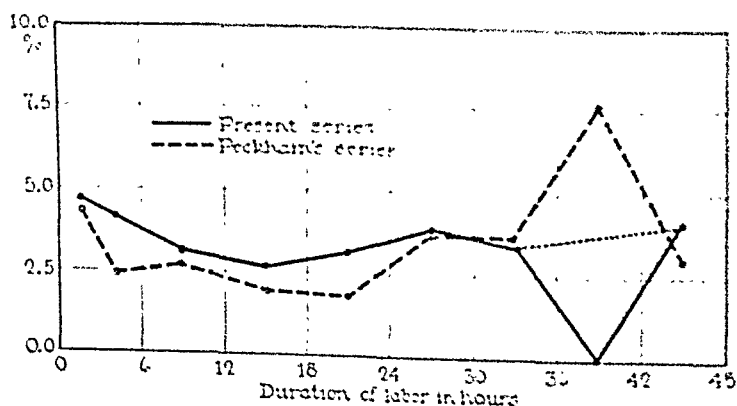


Fig 3 Fetal Mortality in relation to Duration of Labor  
Spontaneous Deliveries



groups of cases, the ratio of Diff./S.E. of Diff. is less than two, the probability is over 5 in 100 that the difference is due to chance. The smaller this ratio becomes, the greater the probability that the difference might be due to chance, as, for instance, when the ratio is one, the probability is 32 in 100. As the standard error of the difference is always greater than the standard error of either one of the quantities, those samples in which there is definitely no significant difference demonstrable may be eliminated by a mere inspection of the percentages with their standard errors.

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Fig. 2 Fetal Mortality in relation to Duration of Labor  
Total Cases at Term

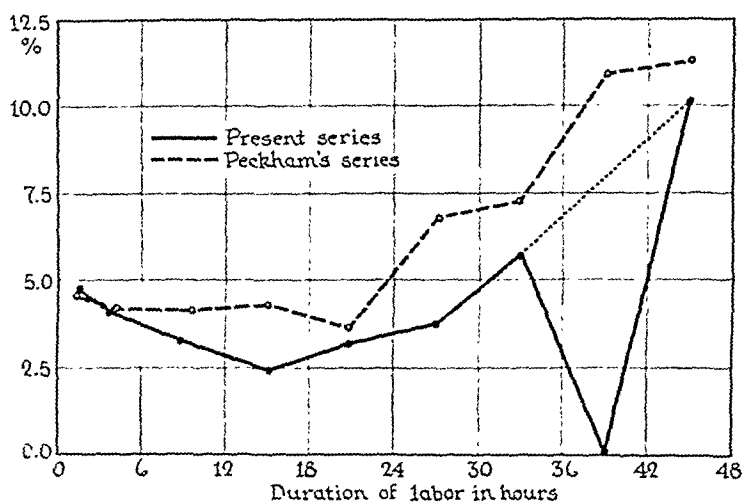
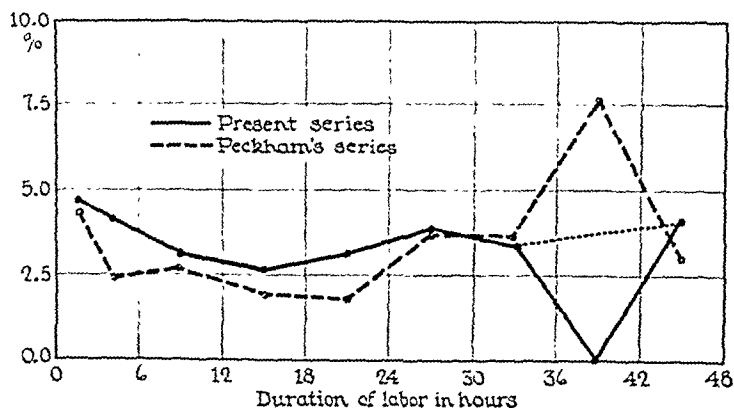


Fig. 3 Fetal Mortality in relation to Duration of Labor  
Spontaneous Deliveries



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Deaths occurring after twenty-four hours did not show any significant difference in rate in relation to the duration of labor.

Operative cases showed a much higher mortality in labors of over forty-two hours than those below forty-two hours. The samples are not large, however, and the difference, 20.51 per cent, could still occur 9 times in 100 chances, but the difference is strongly indicative of being a real one.

Fig. 4 Total Mortality in relation to Duration of Labor  
Spontaneous and Operative Deliveries

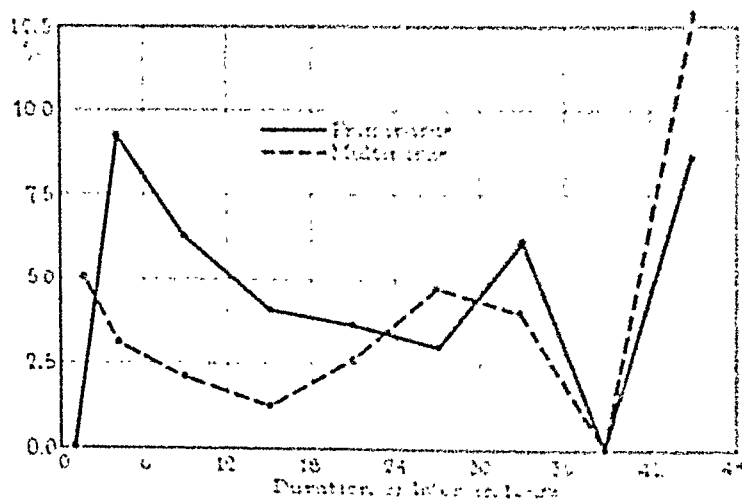
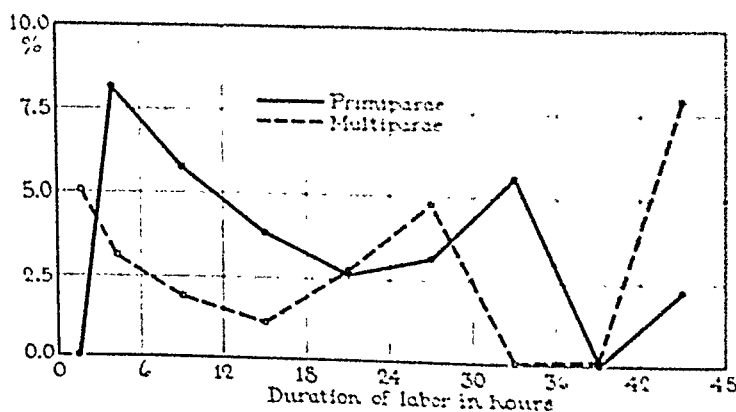


Fig. 5 Total Mortality in relation to Duration of Labor  
Spontaneous Deliveries only



Figs. 4 and 5 represent graphically, the mortality rates in relation to the duration of labor in primiparas and multiparas. The general level is seen to be lower for multiparas than primiparas, with the exception of a few groups, in which cases the difference was found to be not significant by probability determinations. Comparing primiparas and multiparas as a total group, there was a difference of 2.51 per cent  $\pm$  0.85 per cent, the probability being found at 3 in 1,000, and hence showing a definitely significant difference. For spontaneous deliveries alone, a difference of 1.90 per cent  $\pm$  0.82 per cent was found

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Fig. 4. Fetal Mortality in relation to Duration of Labor Spontaneous and Operative Deliveries

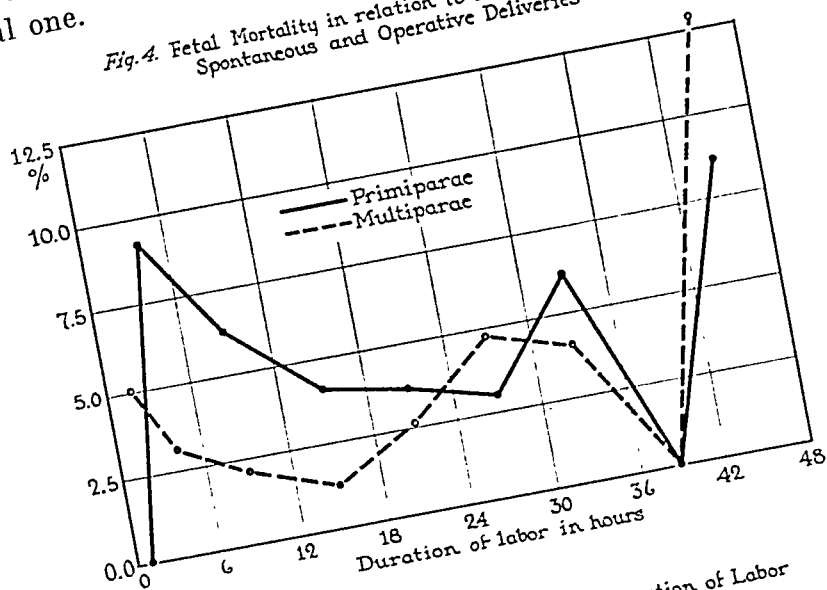
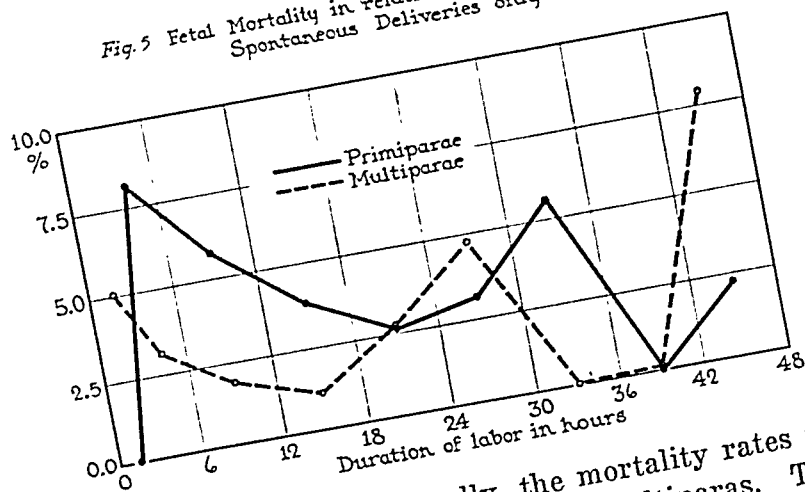


Fig. 5. Fetal Mortality in relation to Duration of Labor Spontaneous Deliveries only



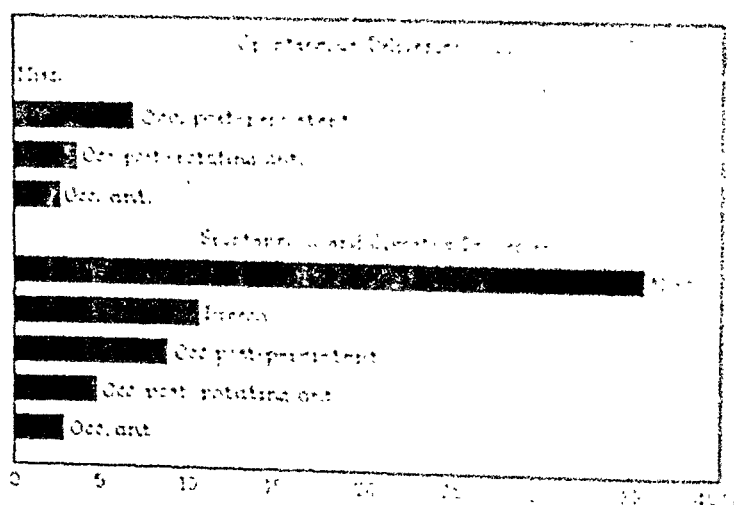
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The probabilities of the differences of the several groups using total deaths are as follows:

		EARLY DEATHS	LATE DEATHS
Occ. ant.	2.81% $\pm$ 0.35%		
Occ. post. to ant.	4.85% $\pm$ 1.49%	1.91% $\pm$ 1.51%	10 in 100
Occ. ant.	2.81% $\pm$ 0.35%		
Occ. post. persistent	8.91% $\pm$ 2.83%	6.19% $\pm$ 2.85%	5 in 100
Occ. ant.	2.81% $\pm$ 0.35%		
Breech	10.53% $\pm$ 1.96%	7.72% $\pm$ 1.97%	6 in 100
Occ. ant.	2.81% $\pm$ 0.35%		
Miscell.	35.71% $\pm$ 12.81%	32.9% $\pm$ 12.81%	1 in 100

FIG. 7. Total Deaths in Relation to Position.



The occiput anterior cases showing the lowest rate, occiput posterior rotating anterior, next, then persistent occiput posterior, finally, breech and miscellaneous. The probabilities as determined show the differences to be significant, only the occiput posterior rotating anterior group having a rather high probability. The rates vary in the same manner as a series reported by Harer (*AM. J. OBST. & GYNEC.* 24: 372, 1933) who found the following: occiput anterior, 2.77 per cent; occiput posterior, 11.35 per cent; breech, 12.62 per cent.

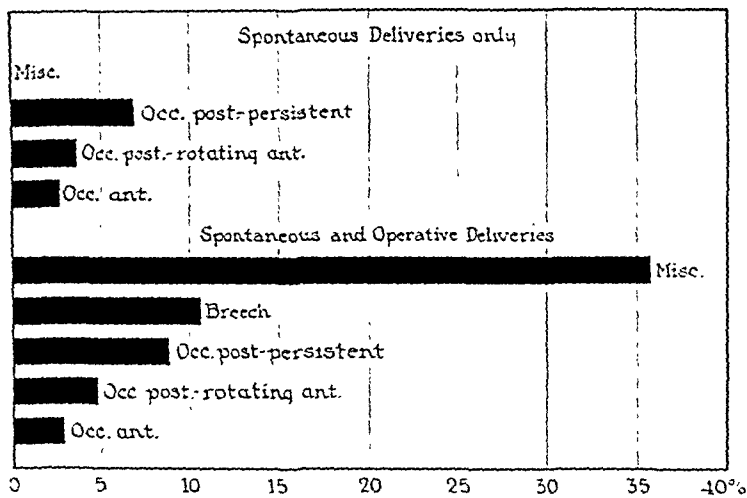
The graph also shows the rate for spontaneous and operative cases and for deaths occurring under twenty-four hours. For spontaneous cases, the general distribution is the same. For operative cases, the number is too small to draw final conclusions, as inspection of the standard errors shows. For deaths occurring under twenty-four hours, the numbers have become too small to draw conclusions. It would appear that the occiput posterior group shows a higher mortality rate in the later deaths than in early deaths.

Breech deliveries show a definitely higher mortality rate which is in general agreement with other published reports. The higher rate is mostly manifested in the early deaths rather than in delayed deaths.

The probabilities of the differences of the several groups using total deaths are as follows:

		DIFFERENCES	PROBABILITY
Occ. ant.	2.81% $\pm$ 0.35%		
Occ. post. to ant.	4.85% $\pm$ 1.49%	2.04% $\pm$ 1.53%	18 in 100
Occ. ant.	2.81% $\pm$ 0.35%		
Occ. post. persistent	8.91% $\pm$ 2.83%	6.10% $\pm$ 2.85%	3 in 100
Occ. ant.	2.81% $\pm$ 0.35%		
Breech	10.53% $\pm$ 4.06%	7.72% $\pm$ 4.07%	6 in 100
Occ. ant.	2.81% $\pm$ 0.35%		
Miscell.	35.71% $\pm$ 12.81%	32.9 % $\pm$ 12.81%	1 in 100

Fig.7 Fetal Deaths in relation to Presentation



The occiput anterior cases showing the lowest rate, occiput posterior rotating anterior, next, then persistent occiput posterior, finally, breech and miscellaneous. The probabilities as determined show the differences to be significant, only the occiput posterior rotating anterior group having a rather high probability. The rates vary in the same manner as a series reported by Harer (*AM. J. OBST. & GYNEC.* 24: 372, 1933) who found the following: occiput anterior, 2.77 per cent; occiput posterior, 11.35 per cent; breech, 12.62 per cent.

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## BARBITURATES IN PRIMIPAROUS LABORS\*

JOHN E. TRETSCH, M.D., AND RICHARD BROWN, M.D., New York, N. Y.

*(From the Department of Obstetrics and Gynecology of the  
Metropolitan Hospital)*

IN THE last decade certain drugs of the barbiturate group have come to the fore as analgesics in labor, but their use has met with such varying degree of success that in the maze of literature on the subject, proper evaluation of results is difficult.

Two particularly common errors are avoided in this study of 185 primiparas at the Metropolitan Hospital: (1) instead of investigating only one, several barbiturates were compared; (2) barbiturates were not used alone, but in combination with other analgesic or anesthesia producing drugs.

This latter error was forcibly brought to our attention at the beginning of this work, when we used a barbiturate alone in our first series of cases. Our results in this series, as we will presently show, were disappointing. However, when we used various barbiturates in conjunction with other drugs we found the apparent accentuation and prolongation of their action to be of inestimable value. For some time it has been evident that this occurred in the preliminary administration of a barbiturate prior to a general anesthetic, where only a minimal amount of anesthetic was then required.

In connection with the first error mentioned, we decided that a combination of several barbiturates with other drugs in small series, observed by the same individuals and compared, would give a fairer basis for evaluation of results. We also felt that better comparison could be made by using only women having their first labors, allowing more prolonged observation and uniformity. All estimates were made by two persons, the resident and assistant resident in obstetrics and gynecology, both of whom are well qualified.

The barbiturates and adjuvant drugs used were as follows:

1. Diallylbarbituric acid (Dial).
2. Sodium isoamylethyl barbiturate (sodium amytal) and morphine.
3. Sodium isoamylethyl barbiturate (sodium amytal) and rectal ether.
4. Sodium allylisopropyl barbiturate (sodium alurate) with pantopon.
5. Sodium allylisopropyl barbiturate (sodium alurate) with scopolamine.
6. Barb-eth-oil.

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\*Read before the Section on Obstetrics and Gynecology of the New York Academy of Medicine, May 22, 1934.

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Before proceeding with the results obtained in three groups of cases, it would be well first to give definitions of terms used in connection with the various items of comparison.

1. Analgesia was necessarily almost entirely objective, inasmuch as the patient having complete or even partial amnesia was incapable of expressing an acceptable opinion as to the amount of pain she suffered. *Good analgesia* implied very little or no response to contractions of the uterus. *Fair analgesia* involved some reaction, such as changing position or slight outcry, but definitely less than would be expected in the average patient without drug administration. *Poor analgesia* meant little or no difference in response from that expected without drug administration.

2. Amnesia depended on enumeration of events by the patient from the time of administration of the drug to the time of delivery, inclusive. *Complete* implied

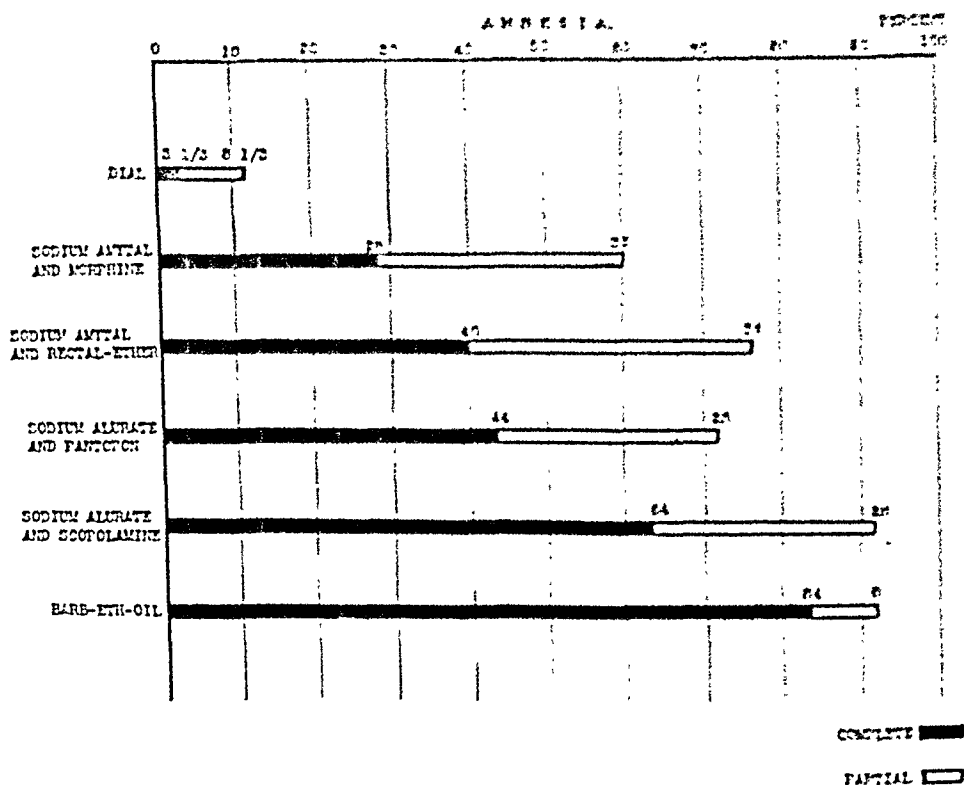


FIG. 2.

absolutely no recollection of events during the above period. *Partial* implied incomplete or hazy recollection of events of the period.

3. Excitement was judged by the amount of physical activity evidenced by the patient: *Marked* excitement required restraint. *Moderate* involved some muscular restlessness but not sufficient to require restraint. *Slight* was not sufficient to give trouble, but implied occasional change of position or slight muttering.

4. Apnea meant that the infant was born not breathing and required some resuscitative measures to stimulate this function, although in all the cases only the tracheal catheter was necessary.

#### ROUTINE

We began the administration of analgesia when labor was definitely established. The criteria were: (1) Dilatation of the cervix to 2

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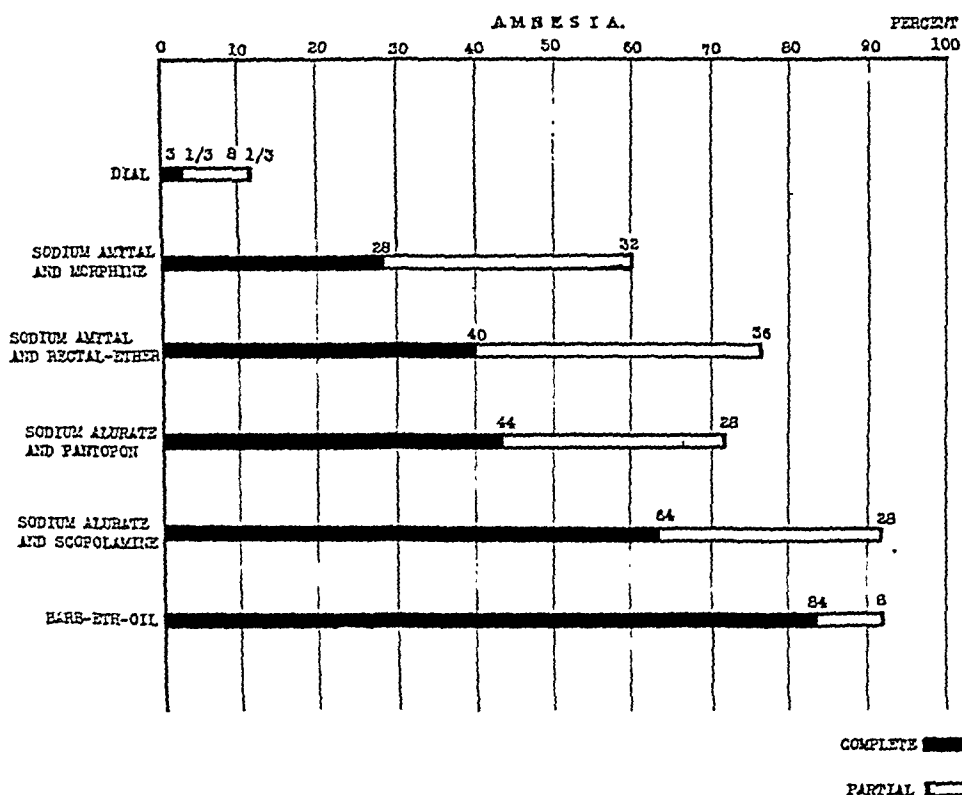


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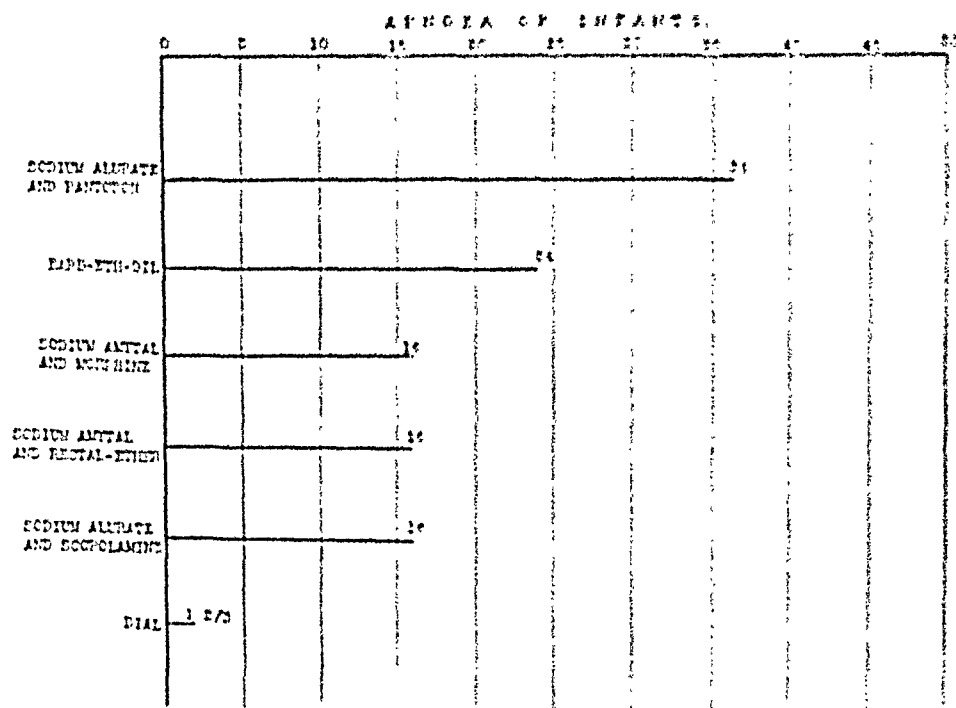


FIG. 4.

There were 60 cases in this series and the details were as follows:

Twenty-six patients received 2 c.c., 17 patients received 4 c.c., 9 patients received 6 c.c., 7 patients received 8 c.c., and 1 patient received 10 c.c.

Average age twenty-two years. Average duration of labor 16.8 hours. Average duration of labor following medication 6.05 hours.

**Delivery:**

Spontaneous	54 cases
Forceps	2 cases
Breech extraction	2 cases
Lacerations of perineum	17 cases
Episiotomies	16 cases

**Analgesia:**

Good	13 cases	21 2/3 %
Fair	29 cases	48 1/3 %
Poor	18 cases	30 %

**Amnesia:**

Complete	2 cases	3 1/3 %
Partial	3 cases	5 %
None	55 cases	91 2/3 %

**Excitement:**

Marked	12 cases	20 %
Moderate	6 cases	10 %
Slight	2 cases	3 1/3 %
None	40 cases	66 2/3 %
Apnea of infant	1 case	1 2/3 %

*Comment.*—Apparently this is a perfectly safe drug, in the dosages used for both mother and infant. It proved so lacking in beneficial results, however, that we felt that barbiturates alone apparently had too little value to warrant their being used without other drugs.

The duration of labor was the longest of any and while the drug afforded some rest for the mother both intra- and postpartum, it did so in only a minor degree as compared with other drugs in the series. It ranks second highest in production of excitement. The technical

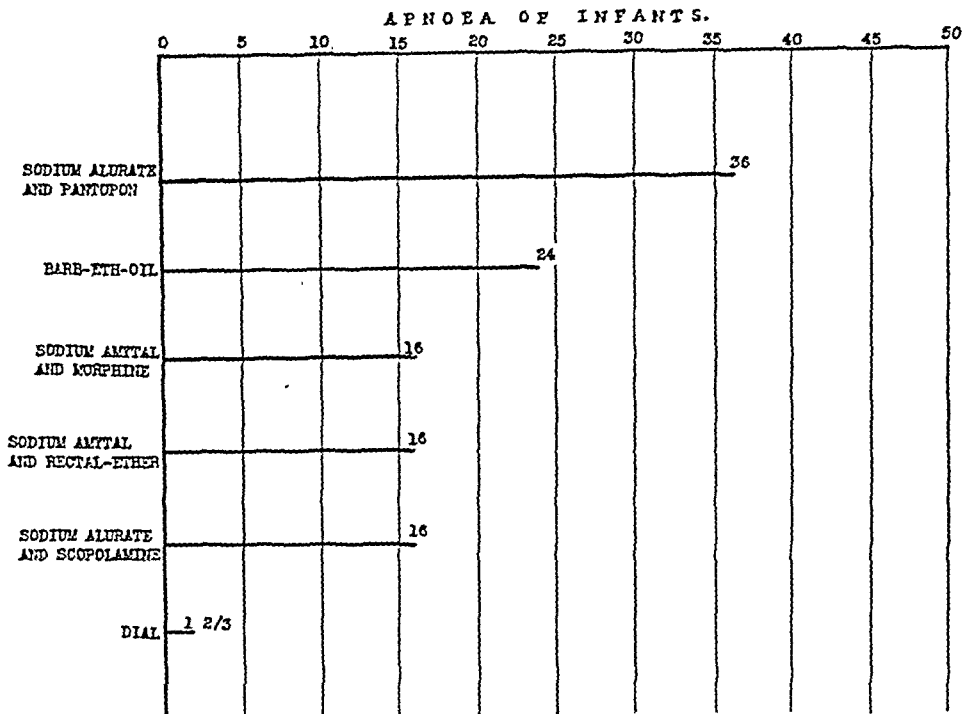


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*Comment.*—This combination of drugs was apparently safe for both mother and infant and the percentage of apnea was relatively low considering the use of morphine. Analgesia was fairly good and amnesia was relatively poor. The duration of labor was not significantly influenced. Excitement was present to such a slight degree that it was not an annoyance.

#### SODIUM ISOAMYLETHYL BARBITURATE (SODIUM AMYTAL) AND RECTAL ETHER

The sodium amytal in this series was administered by mouth simultaneously with the injection by rectum of the ether oil mixture, consisting of ether  $2\frac{1}{2}$  ounces, olive oil  $1\frac{1}{2}$  ounces and quinine sulphate 20 gr.

The amounts of each given were as follows: Ether oil mixture 1 ounce to 21 cases,  $3\frac{1}{2}$  ounces to 2 cases, 3 ounces to 2 cases, and 2 ounces to 1 case; sodium amytal 6 gr. to 17 cases, 9 gr. to 6 cases, 12 gr. to 1 case, and 15 gr. to 1 case.

The dosage of rectal ether was roughly estimated according to the weight of the patient. Average age twenty-two years. Average duration of labor 157 hours. Average duration of labor after medication 8.39 hours.

Delivery:		
Spontaneous	20 cases	
Forceps	2 cases	
Breech extraction	0	
Lacerations of perineum	5 cases	
Episiotomies	12 cases	
Analgesia:		
Good	12 cases	48%
Fair	11 cases	44%
Poor	2 cases	8%
Amnesia:		
Complete	10 cases	40%
Partial	9 cases	36%
None	6 cases	24%
Excitement:		
Marked	1 case	4%
Moderate	6 cases	24%
Slight	11 cases	44%
None	7 cases	28%
Apnea of infant	4 cases	16%

*Comment.*—This combination was safe for both mother and infant. The analgesia produced was slightly better than when morphine was used in place of rectal ether and the degree of amnesia was definitely increased by the latter. The duration of labor was not favorably influenced and the restlessness occurred to about the same degree as in our other rectal ether series. Labor appeared somewhat delayed. The difficulties of administration as well as only average efficiency detract from satisfaction with this method.

#### SODIUM ALLYLISOPROPYL BARBITURATE (SODIUM ALURATE) WITH PANTOPON

In 25 cases sodium alurate was given by mouth in doses of 9 gr. (3 capsules) and immediately thereafter  $\frac{1}{6}$  gr. ( $\frac{1}{2}$  ampule) of pantopon

*Comment.*—This combination of drugs was apparently safe for both mother and infant and the percentage of apnea was relatively low considering the use of morphine. Analgesia was fairly good and amnesia was relatively poor. The duration of labor was not significantly influenced. Excitement was present to such a slight degree that it was not an annoyance.

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The sodium amytal in this series was administered by mouth simultaneously with the injection by rectum of the ether oil mixture, consisting of ether 2½ ounces, olive oil 1½ ounces and quinine sulphate 20 gr.

The amounts of each given were as follows: Ether oil mixture 4 ounces to 21 cases, 3½ ounces to 2 cases, 3 ounces to 2 cases, and 2 ounces to 1 case; sodium amytal 6 gr. to 17 cases, 9 gr. to 6 cases, 12 gr. to 1 case, and 15 gr. to 1 case.

The dosage of rectal ether was roughly estimated according to the weight of the patient. Average age twenty-two years. Average duration of labor 15.7 hours. Average duration of labor after medication 8.39 hours.

Delivery:			
Spontaneous	23 cases		
Forceps	2 cases		
Breech extraction	0		
Lacerations of perineum	3 cases		
Episiotomies	12 cases		
Analgesia:			
Good	12 cases	48%	
Fair	11 cases	44%	
Poor	2 cases	8%	
Amnesia:			
Complete	10 cases	40%	
Partial	9 cases	36%	
None	6 cases	24%	
Excitement:			
Marked	1 case	4%	
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#### SODIUM ALLYLISOPROPYL BARBITURATE (SODIUM ALURATE) WITH PANTOPON

In 25 cases sodium alurate was given by mouth in doses of 9 gr. (3 capsules) and immediately thereafter ¼ gr. (½ ampule) of pantopon

Excitement:		
Marked	5 cases	29%
Moderate	5 cases	29%
Slight	9 cases	25%
None	6 cases	21%
Apnea of infant	4 cases	16%

*Comment.*—This combination of drugs is decidedly satisfactory with the exception of the restlessness, which was the most marked of that in any series and in some cases very troublesome. It is perfectly safe for both mother and child, easy to administer and seems to shorten the duration of labor. The restlessness renders this combination of drugs unsatisfactory for general use, but where sufficient nursing care is available it gives gratifying results. Owing to the amnesia none of these patients have any recollection of their excitement.

#### BARB-ETH-OIL

This preparation is for rectal installation and its formula is as follows:

Ethyl (1 Methyl Butyl) Barbituric acid 8 gr.  
 N-butylethyl barbituric acid (Neomad) 5 gr.  
 Quinine alkaloid 20 grains, ether 2½ ounces  
 Mineral oil 1¼ ounces.

The technical difficulties involved in the administration of this preparation are such that its utilization for general purposes is doubtful. We followed the directions suggested by the manufacturers with the result that expulsion was the rule rather than the exception. The technic recommended by them is as follows: "Plain or soapsuds enemas are given until the return is clear; 2 are usually sufficient. About one ounce of plain mineral or olive oil is allowed to flow into the colon and then the barb-eth-oil is added. When the last of the barb-eth-oil has passed the funnel add about one ounce of plain oil."

In the majority of cases here presented it was our practice to give no enemas with the exception of the one on admission. As a rule the barb-eth-oil was not given until several hours later when colonic and rectal irritability had ceased. The addition of an ounce of oil before and after instillation of the barb-eth-oil is superfluous and only allows an increased volume for retention and greater likelihood of expulsion. The use of oil in addition to that in the mixture was discarded. With the adoption of the altered technic expulsion was exceptional. The dosage roughly corresponds to the patient's weight as follows:

130 pounds or over give 4 fluid ounces  
 100 to 130 pounds give 3 fluid ounces  
 100 pounds or less give 2 fluid ounces.

The amounts given in this series were as follows:

4 ounces in 15 cases  
 3½ ounces in 7 cases  
 3 ounces in 1 case  
 2½ ounces in 2 cases

Excitement:		
Marked	5 cases	20%
Moderate	5 cases	20%
Slight	9 cases	36%
None	6 cases	24%
Apnea of infant	4 cases	16%

*Comment.*—This combination of drugs is decidedly satisfactory with the exception of the restlessness, which was the most marked of that in any series and in some cases very troublesome. It is perfectly safe for both mother and child, easy to administer and seems to shorten the duration of labor. The restlessness renders this combination of drugs unsatisfactory for general use, but where sufficient nursing care is available it gives gratifying results. Owing to the amnesia none of these patients have any recollection of their excitement.

#### BARB-ETH-OIL

This preparation is for rectal installation and its formula is as follows:

Ethyl (1 Methyl Butyl) Barbituric acid 8 gr.  
 N-butylethyl barbituric acid (Neonal) 5 gr.  
 Quinine alkaloid 20 grains, ether 2½ ounces  
 Mineral oil 1¼ ounces.

The technical difficulties involved in the administration of this preparation are such that its utilization for general purposes is doubtful. We followed the directions suggested by the manufacturers with the result that expulsion was the rule rather than the exception. The technic recommended by them is as follows: "Plain or soapsuds enemas are given until the return is clear; 2 are usually sufficient. About one ounce of plain mineral or olive oil is allowed to flow into the colon and then the barb-eth-oil is added. When the last of the barb-eth-oil has passed the funnel add about one ounce of plain oil."

In the majority of cases here presented it was our practice to give no enemas with the exception of the one on admission. As a rule the barb-eth-oil was not given until several hours later when colonic and rectal irritability had ceased. The addition of an ounce of oil before and after instillation of the barb-eth-oil is superfluous and only allows an increased volume for retention and greater likelihood of expulsion. The use of oil in addition to that in the mixture was discarded. With the adoption of the altered technic expulsion was exceptional. The dosage roughly corresponds to the patient's weight as follows:

130 pounds or over give 4 fluid ounces  
 100 to 130 pounds give 3 fluid ounces  
 100 pounds or less give 2 fluid ounces.

The amounts given in this series were as follows:

4 ounces in 15 cases  
 3½ ounces in 7 cases  
 3 ounces in 1 case  
 2½ ounces in 2 cases

*Comment.*—The effect of this drug is so profound that it produces prostration of the mother at times. There were 2 cases of postpartum hemorrhage in this group and the lack of response to remedial measures was alarming. Patients were almost uniformly drowsy for at least forty-eight hours following medication. From the standpoint of analgesia and amnesia this was the best group. Labor seemed to be slightly shortened. There are definite technical difficulties in the administration, and it requires complete cooperation of the patient. Were it possible to exclude the toxicity of this combination of drugs the results would be very satisfactory.

#### CONCLUSIONS

1. Barbiturates used alone apparently are of less value for the relief of pain during labor and for the production of amnesia in labor than they are when combined with certain other drugs.

2. Barbiturates combined with sedative or amnesia-producing drugs appear to accentuate and prolong their action.

3. The drugs used in these series produced no serious or permanent effects on either mother or child.

4. The labors were shortest in the patients in whom the greatest degree of analgesia and amnesia were observed.

5. Ether per rectum used in conjunction with the barbiturates appears to delay labor to a degree.

6. Barbiturates are excitants in about 25 per cent of all cases, and this condition is aggravated by the use of another excitant such as scopolamine, and lessened by sedatives such as pantopon and morphine.

7. Apnea in the infants is more common when barbiturates are used during labor and is aggravated when pantopon is used in addition.

8. Barb-eth-oil gave the best statistical results but general atony of the patients after recommended doses has the possibility of serious consequences.

9. Considering safety of mother and infant, efficiency in producing analgesia and amnesia, and simplicity of administration, we feel that the combination of sodium alurate and scopolamine produced the most satisfactory results in this series. Excitation produced by this combination is a deterring factor and requires special nursing care.

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changes in the adnexa, and the population of the wards is about equal as to race, it is notable that only 27.6 per cent of the ward patients having an ectopic pregnancy were negroes.

Four of the patients had had a previous ectopic gestation, one six months, one two years, one three years, and one ten years previous to admission.

Pain was the first symptom noted in 40 patients, vaginal bleeding or spotting was the first symptom noted in 42, pain and bleeding in 11, the other histories not stating the initial symptoms. Syncope was noted 12 times, and gastrointestinal symptoms 17 times in association with the other symptoms.

Difficulty was encountered in attempting to correlate the menstrual history with the onset of symptoms. This could be done in only 46 cases, and in these the menstrual history was clearly stated, or was the time of onset of symptoms after the normal menstrual period.

Weeks	1	2	3	4	5	6	7	8	9	10	12
Cases	6	8	5	7	5	2	5	2	6	1	1

It will be noted that symptoms occurred in the majority of these patients within nine weeks of the last menstrual cycle.

In 27 patients the leucocyte count was below 8,000; in 9 it was not taken. The remaining patients showed a leucocytosis above 8,000, in showing a count above 20,000. Consequently 65 per cent of the patients showed a leucocytosis.

The Friedman test for pregnancy was done 13 times, being positive 10 times, and negative 3 times in this series. It was also done in a case of abdominal pregnancy in which the child was removed and the placenta left in situ, and was negative before the operative removal of the placenta.

The preoperative diagnosis was as follows:

55 Ectopic pregnancies	} 71, or 74 per cent correct diagnoses excluding 3 cases of abdominal pregnancy near term
17 Tubal ruptures	
2 Tubal abortions	
14 Salpingo-oophoritis	
3 Appendicitis	
1 Threatened abortion	
1 Intrauterine pregnancy with associated fibroids	
1 Abdominal hemorrhage	
1 Twisted ovarian cyst	
1 Cholecystitis	
1 Sarcomatous degeneration of a fibroid uterus	
2 Questionable diagnoses	
1 Not operated	
3 Abdominal pregnancies near term	

It is not possible to obtain statistics relative to the frequency with which ectopic pregnancy was diagnosed, and not found at operation.

In 36 patients the ectopic gestation was on the left side, and in 57 it was on the right side, in 5 it was not stated, and in 4 there were secondary abdominal pregnancies.

Salpingo-oophorectomy or salpingectomy (one case oophorectomy) was performed in all patients, in addition appendectomy in 11, and hysterectomy in 3 for associated fibroids. In 10 patients surgical removal of all or a portion of the opposite adnexa was done for inflammatory conditions.

The final diagnosis was tubal rupture in 47 cases, tubal abortion in 42 cases, untermiated tubal pregnancy in 8 cases, abdominal pregnancy in 4 cases, and ovarian pregnancy in one case. The high incidence of tubal rupture is probably due to the individual operator failing to differentiate between tubal abortion

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5. Sixty-five per cent of the cases showed a leucocyte count.
6. The Friedman test was negative in 23 per cent of the 44 cases in which it should have been positive.
7. The preoperative diagnosis was correct in 74 per cent of the cases.
8. The predominancy of right-sided ectopic pregnancies.
9. Tubal rupture was more frequent than tubal abortion (operative 54 per cent).
10. Total mortality, 2.91 per cent; operative mortality, 1.00 per cent.
11. Blood transfusion was utilized in 26 per cent of the cases.
12. Three cases of advanced ectopic pregnancy, one case of advanced pregnancy, and one case of primary ovarian pregnancy are included in this series.

#### CONCLUSIONS

1. Since the initial symptoms occur before any visible gestation, patients should report early for prenatal care, and should be examined.
2. Cases recognized early and operated upon immediately should recover in most instances.
3. Appendectomy should not be performed in the presence of ectopic pregnancy. We are in accord with the statement published recently by the United States Department of Labor, Children's Bureau: "Maternal Mortality in 15 States" in recommendations under "ectopic pregnancy." "The removal of the appendix in cases of ruptured ectopic is a dangerous procedure and adds to the death from sepsis."

250 SOUTH EIGHTEENTH STREET

## PROPHYLAXIS OF CONGENITAL SYPHILIS\*

JOHN F. COPPOLINO, M.D., PHILADELPHIA, PA.

(From the Pediatric and Obstetrical Departments of the Jefferson Medical College and Hospital)

**C**ONGENITAL syphilis has attracted much attention during the past decade from the standpoint of transmission, treatment, and prophylaxis. It is generally accepted that the transmission of infection to the infant is from the maternal circulation by means of the placenta. It is obvious, therefore, that to prevent the transmission of the disease, measures must be taken to overcome the maternal infection. It follows, then, that the problem is essentially one for the obstetrician and general practitioner.

It has been shown that if a syphilitic woman is actively treated during pregnancy, one may reasonably expect a normal infant, even though the mother's serum reaction remains positive. How then does treatment of the pregnant woman prevent transmission of the disease?

We know that a woman infected in early pregnancy usually gives birth to a dead infant. However, with each succeeding pregnancy there is a tendency for the infection to be less severe until ultimately

\*Read at a meeting of the Obstetrical Society of Philadelphia, November 1, 1934.

5. Sixty-five per cent of the cases showed a leucocytosis.
6. The Friedman test was negative in 23 per cent of the 13 cases in which it should have been positive.
7. The preoperative diagnosis was correct in 74 per cent of the cases.
8. The predominancy of right-sided extrauterine gestation.
9. Tubal rupture was more frequent than tubal abortion (questionable).
10. Total mortality, 2.91 per cent; operative mortality, 1.96 per cent.
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### CONCLUSIONS

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On the first visit, usually at one month of age, each infant is submitted to a complete physical examination including Wassermann and Kahn reactions. If positive, it is requested that each child be returned for further examination. If within three months the serologic tests continue to be positive or if within such time there appear other clinical signs or x-ray evidence of syphilis, the case is considered to be positive. If the tests prove to be negative on the first visit, they are again repeated at three months, six months, one year, and as often thereafter as it is possible to contact the patient.

An analysis of 100 cases is reported. Of these, 30 consist of those women who received no treatment and 70 of those who received a certain amount of therapy during pregnancy. In addition there are at present approximately 50 cases which show the same trend but which have not been followed sufficiently to permit a report.

#### RELATIONSHIP BETWEEN THE TREATED AND NONTREATED WOMEN AND THE FINAL STATUS OF THE CHILD

It was noted that of the 30 infants born of nontreated syphilitic mothers, 24 or 73 1/3 per cent were syphilitic, while eight or 26 2/3 per cent were normal. The morbidity in the offspring of the primiparas was 100 per cent.

On the other hand, in the treated group, there were born 16 or 22.8 per cent infected infants and 54 or 77.2 per cent eventually proved to be nonsyphilitic as attested by negative physical and laboratory findings covering a period from six months to over four years. A striking feature in this group as compared to the former was the marked reduction in the morbidity of the first-born children, falling from 100 per cent to 19.8 per cent.

#### THE EFFICACY OF NEOARSPHENAMINE THERAPY

Thirty-one patients were treated with neoarsphenamine. Nine of these had received treatment in previous pregnancies. The minimum amount employed was 0.8 gm. and the maximum 8.10 gm. Treatment was begun as early as the second month and as late as the ninth month of gestation, but in the majority of cases from the fifth to the seventh month. Thirty infants escaped infection while one proved to be syphilitic. The mother of this child, which is the fourth of five living children, has been under continuous treatment from prior to the first pregnancy up to the present time. At no time has the serum reaction been negative. Why this child should be syphilitic and the others normal is hard to explain.

#### THE EFFICACY OF ACETYLARSAN THERAPY

Thirty-nine were given acetylarsan intramuscularly. Five of these had received treatment in previous pregnancies. The minimum amount given was 6 c.c. and the maximum amount was 46 c.c. Treatment was instituted as early as the second month and as late as the ninth month of pregnancy, but in the majority of instances from the fifth to the seventh month.

Fifteen or 38.4 per cent syphilitic infants were born, while 24 or 61.6 per cent escaped infection, as compared with 3.2 per cent and 96.8 per cent, respectively, in that group which received neoarsphenamine therapy.

Sixteen children proved to be syphilitic despite treatment. It will be observed that in this group, like in the nonsyphilitic group, the time of institution of treatment and the amount given were practically the same. This indicates that no hard

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2028 SOUTH THIRTIETH STREET

## LYMPHOGRANULOMA INGUINALE, CARCINOMA AND SYPHILIS

A TRIAD OF DISEASES OCCURRING IN ONE PATIENT

PHILEAS BERNSTEIN, M.D., NEW YORK, N. Y.

(From the Gynecological Service of the Mount Sinai Hospital)

THIS case is unique for several reasons. It presents a problem in differential diagnosis, since three diseases frequently named as causes for high rectal strictures are involved. It confirms the assumption that lymphogranuloma inguinale spreads through lymphatic channels, thus producing perirectal infiltration. It indicates the importance of the Frei test as a diagnostic aid. It raises the question of the validity of antisyphilitic treatment for rectal stenosis even when a positive Wassermann is reported.

A careful search of the literature reveals no instance in which lymphogranuloma inguinale, squamous cell carcinoma of the cervix and vaginal vault, and syphilis occurred simultaneously in one patient. It is striking in this instance that the final diagnoses of all three diseases rest upon laboratory tests and not clinical observation. Autopsy findings revealed evidence substantiating the results of these laboratory tests.

L. W. (No. 367325), admitted on June 11, 1934; twenty-seven-year-old American negro; gravida i, para 0. In 1932 spontaneous abortion following medication. Admitted with complaints of continuous urinary incontinence, lower abdominal pains and cramps, tenesmus and obstipation; also large painless growths in the skin about the rectum, perineum and vulva.

At the age of seventeen years, sexual contact with a man who was "sick" was followed shortly thereafter by a generalized dermatitis. This disappeared without treatment. Several months later she received four or five bougie treatments for an early rectal stricture which had been causing tenesmus, obstipation, and a purulent intractable rectal discharge. Four years later, a perianal mass appeared; this was tied off and disappeared but several growths returned in its place. Pruritis but no pain was experienced. At the age of twenty-five years, following a positive Wassermann test she received a course of antisyphilitic intravenous and intramuscular injections, which "cleaned up her blood." Symptoms of rectal obstruction were not alleviated, however.

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within the introitus this process formed a thickened smaller band, beyond which the vaginal mucosa was replaced by a hemorrhagic, friable, ulcerated lining of cartilaginous consistency involving the entire cervix and vaginal vault. The transition between this area and the external indurated portion of the vagina was abrupt and marked by a ragged friable hemorrhagic edge. The cervix could not be identified and the anterior vaginal wall throughout was of a leathery consistency. There was profuse bleeding. A vesicovaginal fistula could not be demonstrated upon clinical examination although incontinence was reported.

The perineum and perianal skin was replaced by nodular, hard, rounded elevations, varying from millet seed to walnut size; the bases of these discrete nodules and the



Fig. 2.—Squamous cell carcinoma of vagina or cervix, showing pearl formation below the epithelial level.

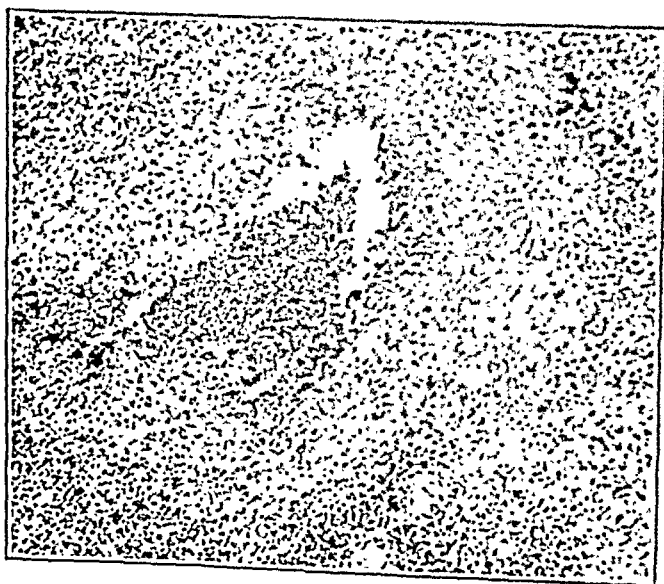


Fig. 3.—Microscopic appearance of the lesion of lymphogranuloma inguinale, showing epithelioid cells in palisade arrangement. This section was taken from a node within the stricture.

smaller, coalescent. Two large raised hard masses were found on either side of the midline just below the Bartholinian openings. To the right and below the anal orifice was a pedunculated egg-sized tumor of almost cartilaginous consistency. In the anal cleft at the mucocutaneous junction, a white hard mass the size of a button extended outward, visible only when the anal folds were separated. The external sphincter was replaced by a keloid ring for a distance of one-half inch.

*Tentative Diagnosis.*—Carcinoma, granuloma inguinale, lymphogranuloma inguinale, and syphilis (history).

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infiltration in three areas was found. (a) An extensive typical lesion of lymphogranuloma inguinale, involving the perirectal tissue, probed marked thickening and stricture, one and a quarter inches proximal to the anus (Fig. 4). The pelvic lymph nodes, in and about the perirectal area were enlarged. Within these nodes the microscope revealed the classical lymphogranuloma inguinale lesion (Fig. 7). (b) The bladder trigone was distorted by lymphogranulomatous invasion and both ureters were obstructed (terminal uremia). (c) The lesions upon the perineum and vulva, as described above (Fig. 1), were also noted in the autopsy protocol. (3) A normal uterus and bilateral adnexal disease were additional findings.

Despite the combined presence of carcinoma and the history of syphilis (both of which may be factors in rectal strictures) ample proof of the etiology in this instance is found in the microscopic evidence. Rarely does the microscopic picture of lymphogranuloma inguinale present itself distal to the primary lesion, particularly within the stricture tissue. This not only confirms the diagnosis of lymphogranuloma inguinale but also the conclusion that spread of the disease occurs through the lymph channels and that the disease produces rectal closure. The highly invasive characteristics of lymphogranuloma inguinale are also observed.

#### DISCUSSION

Before the advent of the Frei test the lesion produced by lymphogranuloma inguinale was usually ascribed to syphilis, gonorrhea, or ulcus molle. This disease has been called tropical bubo, venereal bubo, strumous bubo, nonvenereal bubo, granuloma venereum lymphopathia venereum, condylomata and acuminata, venereal warts, and granuloma inguinale (Donovan bodies). Esthiomene and elephantiasis, which are now known to be the end stages of lymphogranuloma inguinale, were accepted as pathologic entities of unknown etiology. Although lymphogranuloma is by no means a rare disease in America, very little is known about it. It occurs among both white and colored races and has been noted recently in children. A specific test (*Frei cutaneous reaction*) important for its diagnosis, has been evolved. Infection occurs during sexual contact and is caused by a filtrable virus, transferable to monkeys, rabbits, white mice and guinea pigs.

After an incubation period from one to three weeks, infection advances from the symptomless primary lesion into distant, deep or superficial pelvic tissues. The spread from the original site of infection occurs through lymphatic channels. The occurrence of high and low rectal strictures and inguinal bubo is readily understood when the lymph pathways from the primary lesion are considered (Fig. 5).

An initial infection in the portio vaginalis of the cervix or the adjacent vagina usually invades the perirectal tissues, via the uterosacral lymphatic chain; whereas vulvar and perineal primary infections commonly produce a chronic inflammatory local reaction with

infiltration in three areas was found. (a) An extensive typical lesion of lymphogranuloma inguinale, involving the perirectal tissues, produced marked fibrosis and stricture, one and a quarter inches proximal to the anus (Fig. 4). The pelvic lymph nodes, in and about the perirectal scar were enlarged. Within these nodes the microscope revealed the classical lymphogranuloma inguinale lesion (Fig. 3). (b) The bladder trigone was distorted by lymphogranulomatous invasion and both ureters were obstructed (terminal uremia). (c) The lesions upon the perineum and vulva, as described above (Fig. 1), were also noted in the autopsy protocol. (3) A normal uterus and bilateral adnexal disease were additional findings.

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The end stage of the local reaction (testhiomene and elephantiasis) presents a grotesque picture of pedunculated keloid growths, marked edema, fistulas between bladder, rectum, and vagina; ulceration, inguinal bubo, and high and low rectal stricture. Vaginal stenosis is not rare. Infiltration into the bladder floor with complete block of both ureters caused the terminal uremia in this patient.

TABLE I. METASTATIC ROUTES OF LYMPHOGRANULOMA INGUINALE (See Fig. 5)

SITE OF ORIGINAL INFECTION	LOCAL LESION	DISTAL LESION
Perianal skin	Anal stricture	
Vulva	<i>Early lesion:</i> skin thickening with lymph stasis, edema and ulceration <i>Late lesion:</i> testhiomene and elephantiasis	Inguinal adenitis perirectal infiltration (rare)
Perineum		
Clitoris		
Labia		
Introitus		
Cervix	Erosion of mucosa or skin	Perirectal infiltration and stenosis
Vagina		
Rectum		
Vulva		

In the female, rectal obstruction is more frequent than inguinal bubo since the incidence of cervical infection is higher. It is tragic that the earliest symptoms arise after the perirectal lesion is already too far advanced to institute preventive measures. Early activity is recognized only when inguinal adenitis is manifest. In this patient the etiology of the high rectal strictures was uncertain because each of the triad of diseases involved is known to produce stenosis of the distal bowel. Lymphogranuloma inguinale was, however, considered as one of the causes. A diagnostic Frei test may well be utilized in all cases of persistent cervical erosion which fail to yield to usual forms of therapy.

The test, now commonly used in most hospitals, was first described by Wilhelm Frei in 1925. The skin reaction is specific. There are, however, general noteworthy exceptions, which should be borne in mind: (1) In early syphilitic infections occasionally a negative Frei test is obtained, which, if repeated after several weeks of antisyphilitic treatment, becomes positive. (2) Lymphogranuloma inguinale sometimes, however, gives a positive Wassermann reaction even though prolonged and careful search reveals no evidence of syphilis. In this instance, the patient received antisyphilitic treatment for rectal stricture on the basis of a four-plus Wassermann bringing up the question of this exception of the Frei test. It is conceivable, therefore, that this patient may not have had syphilis even though the Wassermann test was positive. (3) An immunologic subgroup of lymphogranuloma inguinale which is Frei negative is found. The vaccine from this

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## SYMPUS APUS, WITH ASSOCIATED TRUNCUS ARTERIOSUS COMMUNIS

WARREN C. HUNTER, M.D., AND HARRY E. MACKEY, M.D.,  
PORTLAND, ORE.

(From the Departments of Pathology and Obstetrics, University of Oregon  
Medical School)

CASE 1.—The mother of the monster was a healthy primipara, eighteen years of age, who entered Multnomah County Hospital in the early first stage of labor. From the history it appeared that the pregnancy had been uncomplicated and should have been at full term, although the uterine fundus was only 29 cm. above the symphysis. The fetal head was already engaged; the fetal heart tones were audible, regular, and had a rate of 132 per minute. The first stage of labor lasted for fifty hours. At the beginning of the second phase the mother seemed distressed and the fetal heart became slow and weak. Thereupon the woman was prepared for immediate delivery and with the aid of low forceps the fetus was extracted easily. The baby gasped for breath a few times and shortly thereafter the heart ceased to function.

*Necropsy.*—The body was that of a monster possessing a solitary lower extremity leading off in a tapering fashion from the trunk and at nearly a right angle to it. The body weight was 820 gm. and the total length 32 cm., the lower extremity contributing 11 cm. The head impressed one as being small in comparison to the trunk. The anterior fontanel was small and the posterior opening was already closed. The skin of the hands was greatly wrinkled. To the left of the midline of the back was a small ulcer of the skin and projecting through it was one of the misplaced sacral vertebrae. There was neither an anus nor external genitalia.

The lower extremity could be flexed anteriorly so that the distal end entered the mouth but extension was very limited. At first the limb resembled a thigh but at about the junction of the middle and distal thirds it began to taper rapidly to a point without any sign of a foot. The circumference of the thigh was 11 cm. while that of the knee was 9 cm. The hip joint was in the midline at the base of an acetabulum situated on the inferior border of the ilium. The ilia were fused, wholly ossified and curved so that when viewed posteriorly the outline resembled one type of a surgical retractor (Fig. 1). Deep in the concavity was a small foramen giving a means of egress for a blood vessel. The ischia were not identified. The superior rami of the pubis joined anteriorly but the inferior rami fused, projected caudally and ended pointedly anterior and parallel to the femur. The entire pubic portion was cartilaginous. A sacroiliac joint was lacking, the sacral vertebrae lying cephalad and parallel with the ilia and only lightly attached to them. The acetabulum was fully covered by synovial membrane. The ligamentum teres originated near the anterior aspect of the acetabulum, was shaped like an inverted U and inserted on either side of the bevelled surfaces on the sides of the femur. The joint capsule was complete. One centimeter distal to the head of the bone were two equal-sized flangelike bony and cartilaginous structures, situated side by side on the anterior aspect of the femur. The position in relation to the head of the bone suggested that these were trochanters. The femur had a length of 7.5 cm., curved anteriorly and both externally and in cross-sections lacked any ridges or grooves that might indicate fusion of two bones. The tibia was 4.3 cm. long and had a maximum breadth

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CASE 1.—The mother of the monster was a healthy primipara, eighteen years of age, who entered Multnomah County Hospital in the early first stage of labor. From the history it appeared that the pregnancy had been uncomplicated and should have been at full term, although the uterine fundus was only 20 cm. above the symphysis. The fetal head was already engaged; the fetal heart tones were audible, regular, and had a rate of 132 per minute. The first stage of labor lasted for fifty hours. At the beginning of the second phase the mother seemed distressed and the fetal heart became slow and weak. Thereupon the woman was prepared for immediate delivery and with the aid of low forceps the fetus was extracted easily. The baby gasped for breath a few times and shortly thereafter the heart ceased to function.

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turning medially to anastomose over the posterior part of the thigh while others continued caudalward and supplied the various thigh muscles.

*CASE 2.*—The woman who gave birth to this monstrosity was delivered at the Multnomah County Hospital on May 31, 1931, having previously been under observation in the Prenatal clinic for three weeks. According to her computation pregnancy would have terminated about June 20. The mother was a primipara, nineteen years of age, in good health. The pregnancy had been an uneventful one. After being in labor for only four hours a viable male baby was delivered spontaneously, and seventeen minutes later a dead and malformed fetus appeared. The living child was normal in every respect, weighed 2,610 gm. at birth, and when discharged from the hospital was in good physical condition. Its present state is unknown.

*Autopsy.*—The fetus measured 28.5 cm. in length and weighed 680 gm. The body was in a poor state of preservation, particularly the head, which was macerated and distorted. The thorax and upper extremities were well formed although the hands appeared quite broad. Beginning at the costal border the body gradually



Fig. 2.—Roentgenogram of the body of Case 2. The head of the femur is clearly on the right side of the pelvis. Thoracic and lumbar scoliosis are evident.

and progressively tapered to a small ball-like angulated skin-covered point at the distal end of the single extremity which curved anteriorly and somewhat from right to left in relation to the trunk. (Fig. 2.) A few degrees of anterior flexion was possible but the limb could not be extended. Dorsally, just cephalad to the junction of the extremity and trunk was a flattened tail-like mass measuring 1.5 by 1.2 cm. and consisting of skin and connective tissue. Both the genital organs and the anus were absent.

The eyes were flattened superior-inferiorly and the cornea of each formed a sharp transversely directed ridge. Attached to the left cornea was a ribbonlike fibrous band 2 to 3 mm. in width and 7 mm. long. The opposite end was free, and there was no way of determining whether it was attached to the fetal membranes or elsewhere. The orbits were fully formed although the left lacked a crystalline lens.

The solitary femur had a length of 6.8 cm., and its anatomy was that of a normally developed bone. The hip joint, joint capsule, and ligamentum teres were

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10 by 1.5 cm., bound to that of the normal twin by only a few strands of placental substance, was complete and exhibited only one small anemic infarct. There were two distinct amniotic sacs of unequal size, the smaller having enclosed the monster. The other placenta measured 17 by 15 by 3.5 cm., was grossly unchanged and possessed a normal umbilical cord.

#### COMMENT

An able discussion of various hypotheses which have been advanced to explain the embryologic disturbance responsible for fusion of the lower extremities will be found in Kampmeier's paper to which the reader is referred. Kampmeier found that the most constantly recurring finding in sireniiform monsters reported previously, and present in his case also, was the occurrence of a single umbilical artery originating directly from the norta. He feels that this, so far as the embryo itself is concerned, is the chief cause of the disturbance in sirenomelus and the persistence of the primitive state in the region of the cloaca and urogenital organs.

In our Case 1 both umbilical arteries were present, although one proved to be obliterated and therefore useless. Histologically there is nothing to indicate the age of the occlusion, but it is conceivable that if this took place early the effect might be the same as if the vessel had never formed. Case 2 exemplifies the common finding of a lone umbilical artery originating directly from the norta and replacing the left common iliac trunk.

In common with the observations made in nearly one-half of the instances of symphodia already recorded there was in each of our examples an apparent agenesis of the entire genitourinary system with the exception of the testes.

Up to the present report five instances of sirenomelus have occurred in twin pregnancies. As in our second example the fetuses have all been males and with a single exception the other twin has been reported to be normal.

A point of interest also is the difference in the location of the hip joint. That of Case 1 lay exactly in the midline of the body while in the other monster the joint was clearly on the right side. In both monsters, particularly the second, fusion of the femora, if this really took place, was so perfect that the resultant single bone assumed the form of a normal femur.

In Kampmeier's table of associated anomalies there is no mention of cardiac disturbances. It would thus appear that the existence of a truncus arteriosus communis is unique among monsters of the sireniiform variety.

#### REFERENCES

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The striking feature of the pelvic examination was the discovery of a lobed mass, the size of a hen's egg to the left and posterior to the overhanging posterior cervical lip. It was indurated and fixed, and its presence in the rectovaginal septum was confirmed by rectal examination. Vigorous palpation provoked bleeding because of beginning erosion of the vaginal surface covering the growth. Apart from this finding were noted a rectocele and relaxed perineum; an intact cervix; a uterus normal in size and position; no distinguishable adnexal enlargements. Proctoscopic and roentgenologic studies with barium excluded a lesion of the bowel.

The blood count showed marked secondary anemia; the serology was negative, as was the urinalysis; the sedimentation test was moderately rapid.

The preoperative diagnosis was in doubt. Since the excessive induration and fixation suggested malignancy rather than an inflammatory lesion, diagnostic biopsy was decided upon. Operation by one of us (L. C. S.) was performed Jan. 28, 1933. Following uterine curettage, an incision was made over the mass, and this disclosed

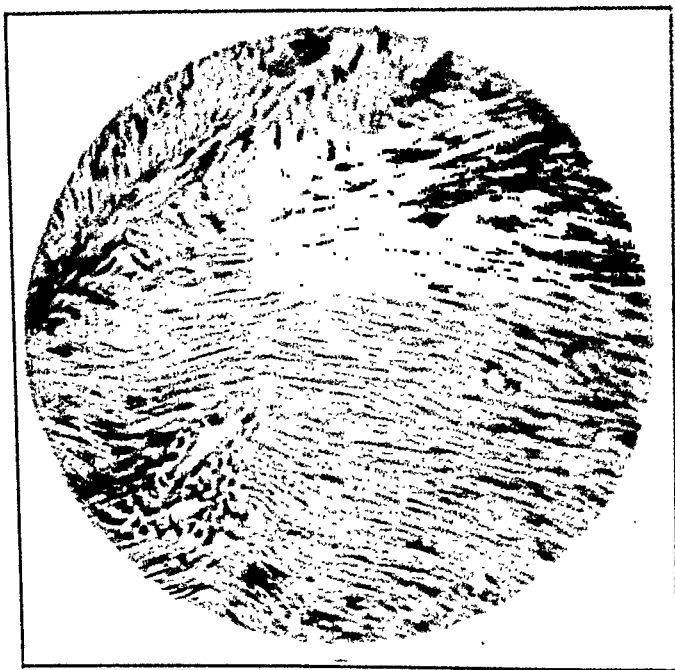


Fig. 1.—Fibromyoma of the rectovaginal septum. Magnification  $\times 500$ .

the possibility of enucleating the growth which proved to be an encapsulated fibromyoma definitely located in the rectovaginal septum. Hemorrhage was controlled by ligature and the incision closed by interrupted sutures.

The tumor weighed 70 gm. and was fairly well vascularized. Histologically, it was a fibromyoma, rather well preserved, but showing mild hyaline changes near the periphery (Fig. 1). Curettings showed premenstrual endometrium. Recovery was complete, the convalescence uneventful.

#### COMMENT

It is curious that but 7 cases, prior to the one just described, were definitely mentioned as originating in the rectovaginal septum. One may speculate as to whether or not all such tumors occurring in the posterior vaginal wall did not originate in the septum primarily. Possibly the size attained by some, the tendency toward extrusion from the vaginal introitus, and the subsequent stretching of the vaginal epithelium over the growth may account for the attributed designation.

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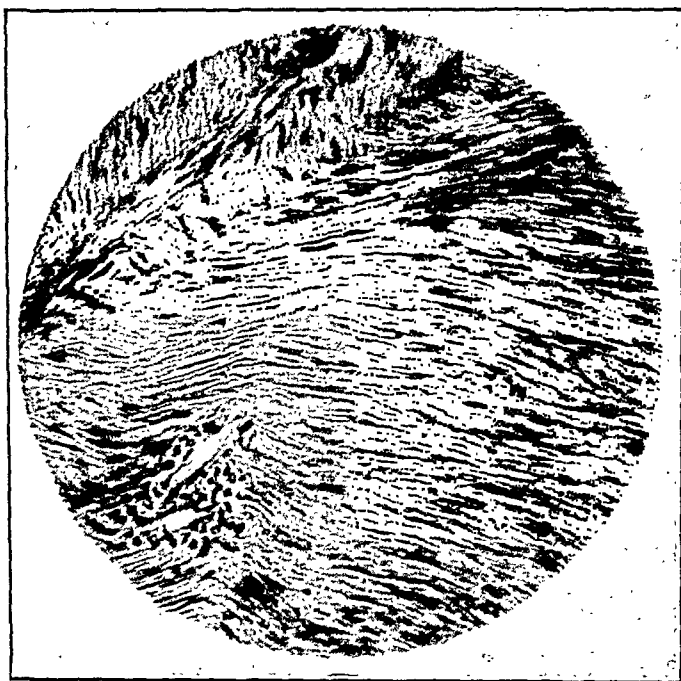


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# A METASTATIC SARCOMA IN A RUPTURED OVARIAN CYST COMPLICATING PREGNANCY\*

CHARLES S. BARNES, M.D., AND FRANK W. KONZELMANN, M.D.  
PHILADELPHIA, PA.

*(From the Obstetrical Department, Temple University Hospital)*

THE patient, a white female, twenty-four years old, was admitted to the Obstetrical wards of the Temple University Hospital in August, 1934, complaining of severe abdominal pain, amenorrhea, and an abdominal tumor.

Her early medical history and family history revealed nothing noteworthy. In October, 1930, her right leg was amputated at the mid thigh because of an osteogenic sarcoma of the tibia, a diagnosis confirmed by microscopic study. Five months later a mass appeared in the right inguinal region. It was excised and upon microscopic examination proved to be only a lymphadenitis without malignancy.

In 1932 the patient was delivered of a normal full-term child. Since then, until four months previous to her admission, she enjoyed good health. In May, 1934 she began to have pain in the right lower abdominal quadrant. It was at first intermittent and slight but by June it became severe and constant. The pain was accompanied by vomiting. She was admitted to the Hahnemann Hospital. There, under treatment, she was relieved and discharged after three weeks. After returning home the pain again appeared and grew increasingly severe. Vomiting became a distressing symptom occurring as often as 12 times in twenty-four hours. It occurred even though the patient abstained from food, but anything swallowed was promptly ejected. On August 23 she was admitted to the Temple University Hospital.

The patient was a Jewess, housewife, married four years. She had had one pregnancy resulting in a normal child now enjoying good health. Her menstrual history was normal until February, 1934. She had not menstruated since.

The patient was well nourished, very pallid, apparently weak, and suffering considerable pain. The abdomen was asymmetrically enlarged. There was tenderness on the right side. Fetal heart sounds were not heard nor fetal movements detected. Fetal parts were palpated with difficulty. Her temperature was 99.8° F., pulse 114, and respiration 28.

The hemoglobin was 4 gm. per 100 c.c. of blood (24 per cent). The erythrocytes were 2,320,000, leucocytes 15,600, of which 21 per cent were immature neutrophils, 64 per cent mature neutrophils, 1 per cent eosinophils, 2 per cent monocytes, and 12 per cent lymphocytes. One nucleated erythrocyte and one myelocyte were found. Urinalysis showed a slight trace of albumin, clumps of pus cells, and a positive test for occult blood.

The temperature and pulse gradually rose. The patient was subjected to abdominal exploratory operation. Large masses of clotted blood were found and readily evacuated. Masses of soft friable tissue resembling placenta and remnants of what appeared to be a thin-walled sac were removed. The uterus was intact. It was not disturbed and after placing a pack and drains in the cavity evacuated, the abdomen was closed. The patient died of what seemed to be abdominal hemorrhage, one-half hour postoperative.

\*Read (by invitation) at a meeting of the Obstetrical Society of Philadelphia, November 1, 1934.

## A METASTATIC SARCOMA IN A RUPTURED OVARIAN CYST COMPLICATING PREGNANCY\*

CHARLES S. BARNES, M.D., AND FRANK W. KONZELMANN, M.D.,  
PHILADELPHIA, PA.

*(From the Obstetrical Department, Temple University Hospital)*

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The retroperitoneal tumor contained considerable osteoid tissue, branching and anastomosing spicules of hyaline tissue having the picture of bone. Other irregular hyaline masses without lamellar arrangement or canaliculi were also seen. Some portions of the tumor were cellular and resembled the tissue found in the wall of the ovarian cyst. The tumor in the pancreas was identical with the retroperitoneal tumor, showing osteoid tissue as well as true bone formation.

The tumor in the lung also showed true bone formation and osteoid tissue. The dermoid cyst of the ovary revealed the usual beautifully arranged stratified squamous epithelium with hair follicles, sebaceous and coil glands. A relatively small amount of recognizable ovarian stroma existed about a corpus luteum. In this stroma a few primordial follicles were encountered.

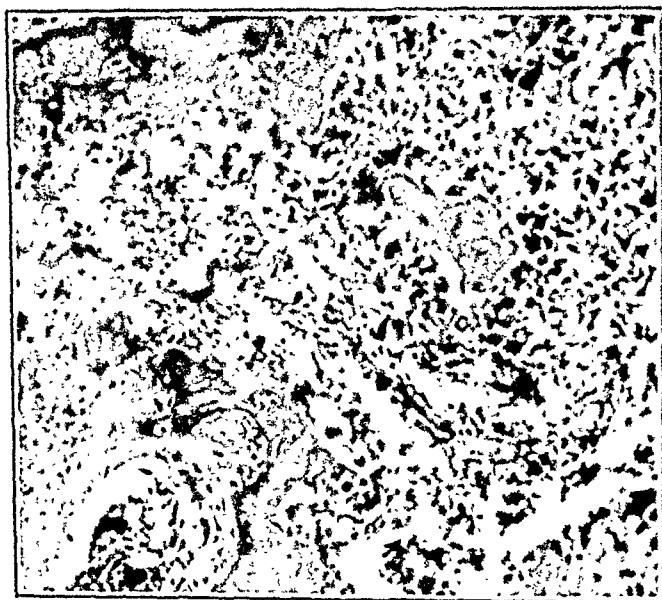


Fig. 2.—A section of the retroperitoneal tumor. This area shows ossification of cartilage, as well as the cellular stroma pictured in Fig. 1. Other parts of the tumor revealed bone formation by osteoblastic activity. The general structure of the primary tumor was much like that pictured in the metastatic lesions.

Subsequent to the autopsy, we obtained the original slides of tissue studied at the time of the amputation of the leg in 1930. The histologic picture is so much like that just described that the section might have been taken from any one of the tumor masses found at the autopsy.

**Conclusion.**—This is a striking example of metastatic sarcoma, arising in a tumor that had been amputated four years previously. The metastatic masses in the lung, in the pancreas and retroperitoneal space were not incompatible with life, and judging from their previous rate of growth, might not have become so for many years. It is also noteworthy that pregnancy occurred after one ovary had been completely destroyed by a tumor and the opposite ovary almost completely replaced by a dermoid cyst.

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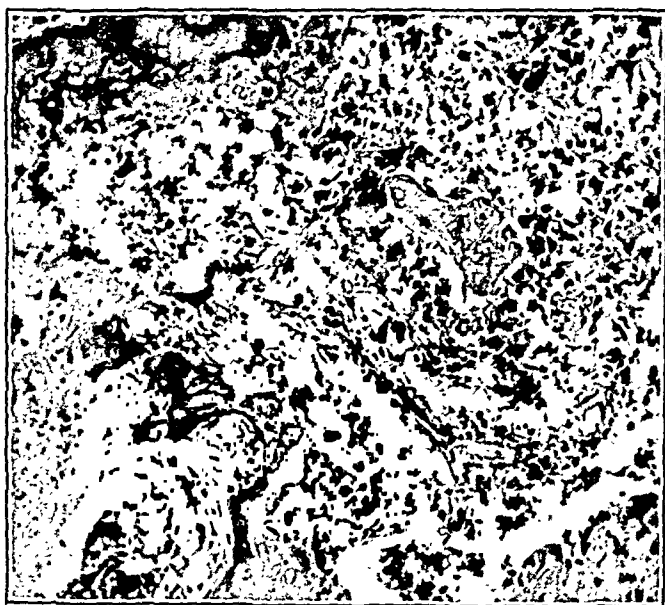


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The salient points connected with this new pessary are:

1. It is made of one solid piece and has a mushroom-like shape. Its upper surface is slightly depressed, its contour is well rounded and, beneath, tapers off into a fairly slender stem which terminates in a flat knob (Fig. 1).

2. The material used is a synthetic resin which, among other ingredients, contains phenol and formaldehyde. This substance appears on the market under various trade names such as bakelite, catalin, marblette, durax, plaskon, and is commercially used in the manufacture of door knobs, gavel, fountain pens, bracelets, etc.

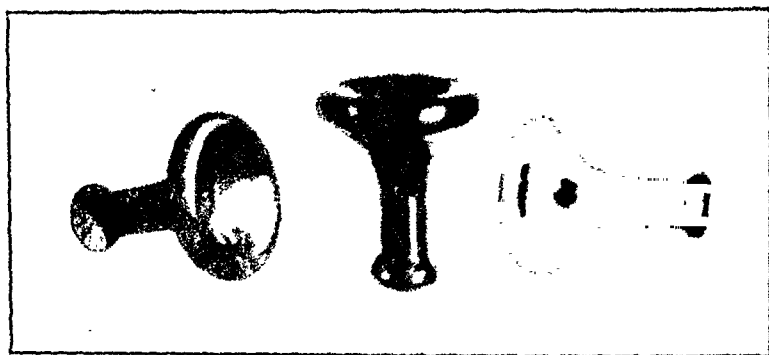


FIG. 1.

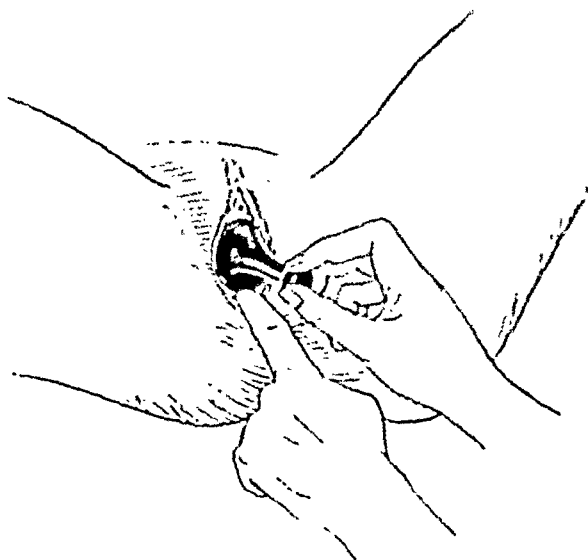


FIG. 2.

3. It is unbreakable and always remains smooth because it is unaffected by the genital secretions. In its turn it does not affect or irritate the vaginal mucosa.

4. It is inserted, well lubricated, edgewise and in an oblique direction, so as to avoid the urethral opening, while the perineum is strongly pushed downward (Fig. 2). It is introduced into the vagina by a corkscrew like motion. Once within the vaginal lumen, the pessary is pushed upward until only the extremity of the stem shows in the vaginal entrance. The appliance then lies transversely beneath the cervix (Fig. 3).

5. The patient removes the pessary *every night* by pulling on the handle of the stem, turning the latter to one side and then reversing the steps described in 4.

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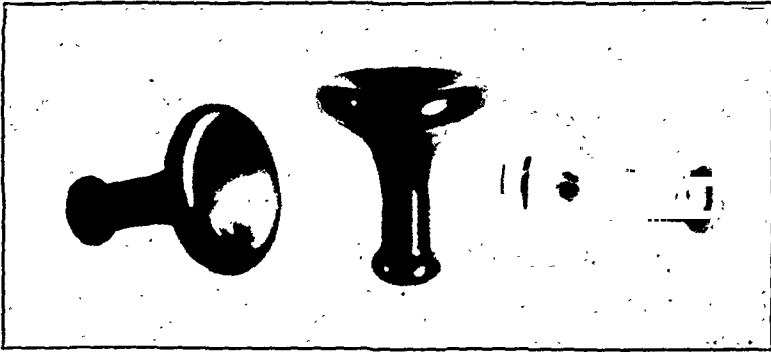


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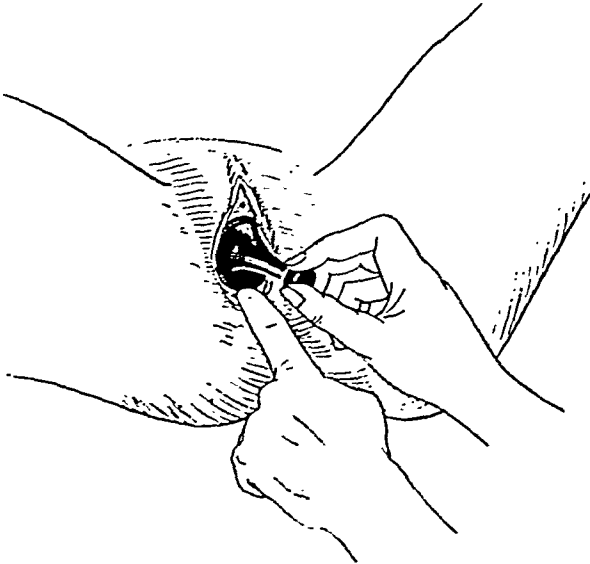


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THE SEX DETERMINATION TEST OF DORN AND SUGARMAN

DAVID S. PANKRATZ, PH.D., MEMPHIS, TENN.

(From the Department of Embryology and Histology, College of Medicine, The University of Tennessee.)

SINCE the appearance of the publication on sex prediction by Dorn and Sugarman<sup>1</sup> I have attempted to duplicate their findings. A few pregnant patients\* were chosen and studied for a number of months. No patients with toxemia were used. Morning urines were obtained at different stages of gestation. The earliest specimen used was that from a patient during the nineteenth week, and the latest during the thirty-ninth week of pregnancy. At various intervals injections of 8 to 10 c.c. of pregnancy urine were made into the ear veins of selected young male rabbits, the testes excised and examined forty-eight hours later. The rabbits were obtained from a registered rabbitry and their exact ages were known. These rabbits were observed for a number of days and used only when the testes were descending, as specified by the original investigators.

In most cases both testes were removed from the control and experimental animals under light ether anesthesia. Each testis was examined macroscopically for enlargement and for engorgement of blood vessels. They were then cut in halves and fixed in Bouin's fixative for twelve hours, followed by routine technic with hematoxylin and eosin staining. Sections were cut at various levels of the testes 4, 6, and 10 micra in thickness. These sections were studied microscopically and the diameter of the seminiferous tubules, the vascularity, and the amount of spermatogenesis noted. One or two controls were run in every case. Table I shows the number of cases studied, the number and time of injections, the sex predicted and the sex of the child.

TABLE I

PATIENT	WEEKS OF GESTATION	MICROSCOPIC PREDICTION	WEEKS OF GESTATION	MICROSCOPIC PREDICTION	WEEKS OF GESTATION	MICROSCOPIC PREDICTION	WEEKS OF GESTATION	MICROSCOPIC PREDICTION	WEEKS OF GESTATION	MICROSCOPIC PREDICTION	SEX OF CHILD
P S D H	19	Male	20	Female	32	Female	36	Male	38	Female	Female
	20	Male	25	Female	29	Female	33	Male			Male
					33	Female	37	Male	39	Female	Female
					34	Female	35	Female			Female

\*Patients of Dr. W. A. Ruch whose courtesy the author wishes to acknowledge.

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## FATALITY AFTER AN INTERPOSITION OPERATION

CLAYTON T. BEECHAM, B.S., M.D., PHILADELPHIA, PA.

*(From the Division of Obstetrics and Gynecology, University of Minnesota)*

THE interposition operation is an ideal procedure for treating uncomplicated proidentia only after the menopause. Litzsberg and Schumann are quite emphatic on this being the primary indication. Many surgeons, however, employ the interposition operation with sterilization during the child-bearing period. With the exception of hysterectomy nearly all methods have been attended with failures. Untoward results follow when the interposition operation and attempted sterilization are followed by pregnancy. The following is the report of a case of this kind which resulted in a series of complications and death of the patient:

Mrs. A. S., aged thirty-eight, admitted in uremic coma to University of Minnesota Hospital, April 19, 1932 and died about seven hours later. The history was obtained from the husband and the records of another hospital. She had ten uneventful pregnancies.

The patient was operated upon Aug. 6, 1929, at an out-of-the-state hospital from which we obtained the following report: "The fundus of the uterus was brought through the opening of the peritoneum. The left tube was freely movable; the right tube was found to be adherent posteriorly, and the right cornu of the uterus could not be brought as far forward as the left. The right tube was cut and ligated near the uterus. The left tube was tied and cut likewise. The fundus of the uterus was then made fast to the pubovesicular fascia with the bladder lying on top of it. The split mucosa was closed together with interrupted chromic gut sutures."

The patient moved into northern Minnesota far from any sort of medical care.

She had her last menstrual period Dec. 20, 1931. In March she began to have difficulty in voiding, but drinking soda and water and walking around enabled her to urinate. This difficulty continued for three weeks.

In April, the difficulty in voiding became more severe; the patient was able to pass only one or two ounces of urine a day. To stimulate urination, warm external douches were given with little help. About this time, she developed abdominal distention, which had been constant and progressive. A few days later the patient became delirious and extremely drowsy.

She was admitted to the University of Minnesota Hospital April 19, 1932 in coma, with Cheyne-Stokes respirations, pulse rapid and thready, uremic odor to breath, and blood pressure 70/0.

The abdomen was markedly distended, with no rigidity. There was fluid present. The uterus was enlarged diffusely and filled the entire pelvic cavity. It was adherent in all directions and was lying between the symphysis and the bladder. General supportive treatment was instituted. The patient was catheterized with some difficulty, as the urethra seemed obstructed; 1,300 c.c. of urine were obtained and it was too bloody to analyze accurately.

The hemoglobin was 72 per cent and W. B. C. 12,600.

The blood chemistry was as follows: Urea nitrogen, 120 mg. per 100 c.c. of blood; nonprotein nitrogen, 204 mg. per 100 c.c. of blood; creatinine, 4.2 mg. per 100 c.c. of blood; and sodium chloride (plasma), 490 mg. per 100 c.c. of blood.

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by a primary union. The lochial discharge throughout the postoperative period was scanty but foul. It was considered that the patient had a mild intrauterine infection which she localized and controlled from spreading outside the uterus. The temperature having been normal for three days, the patient was discharged on the nineteenth postoperative day, April 4, 1932.

She reentered the hospital on Jan. 20, 1933, less than ten months after the previous discharge. Her last menstrual period had occurred on August 14, 1932, five and one-half months before the second admission to the hospital. Ten days before, the patient was suddenly seized with sharp pain in the right lower quadrant of the abdomen. This pain radiated to the umbilicus and was accompanied by vomiting, and right shoulder pain. From then until the time of admission her complaints were those of malaise, slight general abdominal pain, urinary frequency, diarrhea, and slight elevation of temperature. During this time she was under the care of her family doctor who treated her for "intestinal grippe." However, the patient noticed that her abdomen had become smaller and that her breasts had enlarged considerably. On admission to the hospital her temperature was normal and pulse was 96. The next day the temperature rose to 100.6°, pulse varied between 96 and 100. The uterus was felt to extend midway between symphysis and umbilicus and there was tenderness and spasticity over the lower abdomen and flanks. On the right side a vague mass extending to above the umbilicus could be made out. The culdesac and left adnexal region were clear, but in the right fornix there was an indefinite mass whose upper border could not be defined. A diagnosis of rupture of the uterus with extrusion of the fetus was made and x-ray examination corroborated this by revealing the fetus lying in the right upper quadrant of the abdomen.

At operation the peritoneal cavity contained a considerable quantity of old dark blood. An unruptured amniotic sac was found in the right upper abdomen, the fetus lying just below the edge of the liver. The sac was opened and a 59 cm. macerated fetus was removed. The placenta was in the right lumbar gutter from the brim of the pelvis to the liver. It was easily stripped from the underlying peritoneum and the maternal surface was found to be covered with a thick layer of organizing blood clot. The rest of the peritoneal surface both visceral and parietal was covered with shaggy remains of organizing blood clot, so that nowhere could the normal shiny peritoneum be seen. The uterus was contracted to the size of a three and a half months' gravidity and widely opened along the entire length of its anterior surface. The supravaginal hysterectomy was performed and two cigaret drains were placed to the pelvis because of the extensive roughness left by the adherent blood clots. The transfusion was given immediately afterward and the postoperative course was quite uneventful.

The pathologic examination of the uterus was reported as showing the following histologic picture of sections taken from the edge of the uterine rupture. "A layer of fibroblasts with young blood vessels and frequent lymphocytes covered by a layer of hemorrhage. The fibrous tissue extends laterally and is rather sharply delimited from the uterine musculature. It is apparent that the rupture occurred at the previous site of trauma to the uterus. The remainder of the myometrium does not present any abnormality. Diagnosis: ruptured uterus at the site of a previous scar."

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was slightly enlarged and deep red in color. The liver was normal in size, gray, foamy and filled with small gas cavities. Kidneys etc markedly congested with markings entirely obscured, but of normal size. The ovaries were large and contained gas cavities. Tubes appeared normal. The uterus was three times normal size with a small piece of adherent tissue in its cavity, and showed no sign of trauma; large gas cysts and dissociated muscle.

The pericardial cavity was distended by the heart which filled it entirely. The heart muscle was pale, stained with "hematin" and filled with gas cavities. The lungs were stained, distended with gas; the right lung was entirely adherent to the parietal pleura.

Culture from the heart, and smears from the liver and uterine cavity showed large numbers of Welch bacilli, straight rods, gram-positive, from 3 to 6 micra in length with slightly rounded or square cut ends; capsules were demonstrated.

#### COMMENT

The pathogenicity of the Welch bacillus is extremely variable. A well-known saprophyte, with a wide distribution in nature, it has been observed in the normal vagina. In one case reported by Falls, a woman in the hospital for four weeks, under observation for cardiac disease, aborted spontaneously; the fetus was emphysematous, and smears and culture showed Welch bacillus; there was no temperature previous to or following the abortion. In abortion and after long labor with dead fetus, we too, when gas bubbles were present, have demonstrated the Welch bacillus, and have administered prophylactic serum. None of these patients has shown any unusual morbidity. Wrigley, who has made a thorough bacteriologic investigation of the subject, believes that dead tissue must be present. For practical purposes, since the condition becomes serious only when the musculature of the uterus is invaded, it is probable that the organism acts only as a saprophyte, unless its introduction is associated with muscle trauma and the presence of dead tissue. Despite the history, serious gas sepsis in abortion should indicate induction.

Unusual pain, high leucocytosis, hemoglobinuria, rapid pulse, and particularly icterocyanosis is diagnostic of gas bacillus sepsis.

Hysterectomy, transfusion, and serum have of course their place in treatment. Prophylaxis is most important.

256 JEFFERSON AVENUE

Taylor, A. B.: Vesico-Vaginal and Kindred Fistulas. South African M. J. 8: 570, 1934.

There is much greater incidence of vesicovaginal fistulas in South Africa because of poor obstetrics. Most of the deliveries are effected by midwives. The etiology is due to (1) mechanical injury, cutting instruments (broken bottle), forceps, tight abdominal binder, etc.; (2) intravesical pressure, due to postpartum urine retention and thus a devitalization of tissues; and (3) sepsis.

Only a small percentage of cases heal without operation. Unhealed operations do not prevent the occurrence of a pregnancy. There are few fistulas that are inoperable. The author advises much better training of midwives and suggests that fistulas occur when too many friends and native doctors examine the patient. He advises free episiotomies, craniotomies on all dead babies, and urinary antiseptics postpartum. Operation should be done only after urine is made acid. He prefers the double flap operation except in those cases where there are small fistulas, thick margins and a good blood supply. Incision of vaginal mucosa should be in direction of long diameter of the fistula. Thorough infiltration with a weak solution of adrenalin will prevent most of the bleeding.

F. L. ADAIR AND I. BROWN.

was slightly enlarged and deep red in color. The liver was normal in size, gray, foamy and filled with small gas cavities. Kidneys were markedly congested with markings entirely obscured, but of normal size. The ovaries were large and contained gas cavities. Tubes appeared normal. The uterus was three times normal size with a small piece of adherent tissue in its cavity, and showed no sign of trauma; large gas cysts and dissociated muscle.

The pericardial cavity was distended by the heart which filled it entirely. The heart muscle was pale, stained with "hematin" and filled with gas cavities. The lungs were stained, distended with gas; the right lung was entirely adherent to the parietal pleura.

Culture from the heart, and smears from the liver and uterine cavity showed large numbers of Welch bacilli, straight rods, gram-positive, from 3 to 6 micra in length with slightly rounded or square cut ends; capsules were demonstrated.

#### COMMENT

The pathogenicity of the Welch bacillus is extremely variable. A well-known saprophyte, with a wide distribution in nature, it has been observed in the normal vagina. In one case reported by Falls, a woman in the hospital for four weeks, under observation for cardiac disease, aborted spontaneously; the fetus was emphysematous, and smears and culture showed Welch bacillus; there was no temperature previous to or following the abortion. In abortion and after long labor with dead fetus, we too, when gas bubbles were present, have demonstrated the Welch bacillus, and have administered prophylactic serum. None of these patients has shown any unusual morbidity. Wrigley, who has made a thorough bacteriologic investigation of the subject, believes that dead tissue must be present. For practical purposes, since the condition becomes serious only when the musculature of the uterus is invaded, it is probable that the organism acts only as a saprophyte, unless its introduction is associated with muscle trauma and the presence of dead tissue. Despite the history, serious gas sepsis in abortion should indicate induction.

Unusual pain, high leucocytosis, hemoglobinuria, rapid pulse, and particularly icterocyanosis is diagnostic of gas bacillus sepsis.

Hysterectomy, transfusion, and serum have of course their place in treatment. Prophylaxis is most important.

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On Nov. 30, 1933, the patient presented herself at my office stating that her last normal period was April 28, 1933. On examination I found the patient to be about seven months pregnant, and I arranged for her to attend the prenatal clinic. She was confined Dec. 30, 1933. The duration of the labor was four hours and the delivery was spontaneous. The baby weighed 5 pounds 23½ ounces. This was no doubt due to the fact that labor began about three weeks prematurely. The baby was vigorous and did well from birth. The placenta came away rather reluctantly at the end of an hour with the help of the Credé method. The puerperal period was normal, and on discharge from the hospital on the fourteenth day after delivery the uterus was well involuted and the pelvis seemed normal.

4 HAYMAN COURT

## MASSIVE UMBILICAL HERNIA WITH ENTEROCYSTOMA IN A NEWBORN

OSCAR GLASS, M.D., NEWARK, N. J.

(From St. Michael's Hospital)

CASES of intestinal cysts have been reported by Casin, Henning and Roth (1884). Colmers in 1906 published an article on intestinal cysts, and according to him, Raesfeld was the first to describe an enterocystoma.

The course of the pregnancy of Mrs. B. M., a twenty-two-year-old primipara, was rather stormy, with hyperemesis, albuminuria, and hypertension, which required repeated hospitalization. Two weeks before the expected date of delivery she went into labor and was delivered of a boy weighing 63½ pounds. Examination of

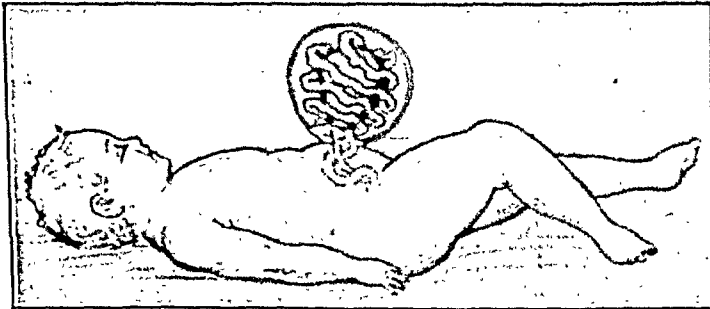


Fig. 1.

the cord before ligation revealed a hernia 12 by 10 by 8 cm., protruding through the umbilicus, thin and transparent with loops of intestines plainly visible through the sac. The cord was tied off distal to the hernia, but because of a mass within the sac all attempts at reduction of the hernia were unsuccessful.

Seven hours after delivery, Dr. Edgar A. III, called in consultation, advised immediate surgical repair. This was done under ether anesthesia, one dram administered in drops. The hernia was opened and examined and the neck of the sac was found to measure 1.5 cm. in diameter. Contained in the sac were several loops of small intestine together with a smooth globular mass of cystic consistency about 5 cm. across and attached to a pedicle which seemed to reach to the root of the mesentery.

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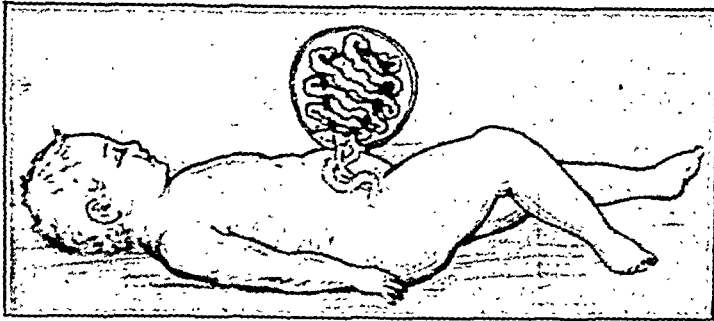


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When the patient is ready for the operation a large size (No. 18 F.) catheter is inserted in the bladder in the usual manner; the jar is laid between the patient's legs and Tube B is connected to the catheter. The rubber tubing and the air bulb pass under the patient's leg to hang down on either side of the operating table under the sterile drapes. The ansterile nurse works the apparatus. The air valve on the bulb is left open for the bladder to empty itself. The air valve is closed when filling the bladder and when the bladder is to stay filled. The air bulb is compressed intermittently every three to four seconds and with each compression about one ounce of fluid enters the bladder. The interval of three to four seconds for re-

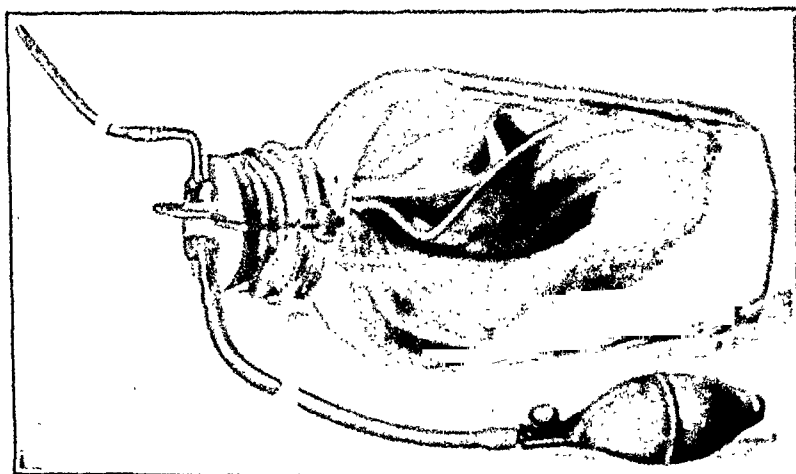


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ing 5) between each compression is necessary to allow the fluid to run into the bladder without excess pressure. The extent to which the bladder is to be distended is determined by watching the bladder while it is being filled. The setting up of the apparatus is very simple, requiring only a few minutes, less time than it takes to describe it. Its very simplicity favors its use.

The apparatus has been recommended also in the cervical cesarean.

The apparatus should be connected as a routine in all lower abdominal and pelvic operations so that if an occasion arises where the bladder needs to be outlined, it can be done so easily and promptly. It is a great satisfaction to be able to distend the bladder before the abdomen is closed and have the assurance that the bladder is uninjured.

15 EAST ONE HUNDRED ELEVENTH STREET

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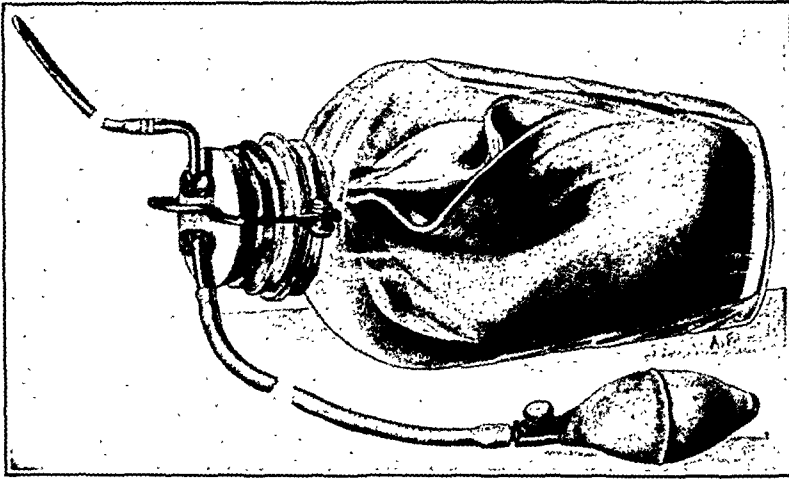


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five months was found free in the abdomen. There was a clean longitudinal rent in the midline of the posterior surface of the uterus extending from the fundus to the level of the internal os. The rupture was so clean and regular in outline that it appeared as if an incision had been made with a knife. The placenta was closely adherent to the anterior wall of the uterus. A subtotal hysterectomy was done, and the abdomen closed without drainage. The fetus weighed 600 gm. and was 32 cm. in length. The patient made a satisfactory postoperative recovery following multiple massive transfusions, and was discharged from the hospital in two weeks.

#### DISCUSSION

It is quite likely that the fall, which the patient had, as well as the previous severe puerperal endometritis should be considered as etiologic factors in this case. The diagnosis of rupture of the uterus in early pregnancy is difficult, and is easily confused with hemorrhage from a ruptured ectopic pregnancy, the clinical picture being essentially that of intrabdominal hemorrhage. The present case illustrates the confusion in the diagnosis of spontaneous rupture in early pregnancy, and although the ultimate result in this instance was satisfactory, valuable time was lost before proper treatment was instituted. When first seen, the patient presented the picture of threatened miscarriage, although incomplete rupture had doubtless occurred at that time.

#### REFERENCES

- (1) *Baisch*: Quoted from Williams Obstetrics, Ed. 6, New York, 1930, D. Appleton Co. (2) *Smylie, R. S.*: AM. J. OBST. & GYNCO, 23: 595, 1932. (3) *Tedlat and Pizzera*: Bull. Soc. d'obst. et de gynéc. 21: 230, 1932. (4) *Spirogl, J.*: Gynäk. 72: 24, 1932. (5) *Hurd, E.*: AM. J. OBST. & GYNCO, 26: 889, 1933.

### A NEW OBSTETRIC FORCEPS

J. E. GARRISON, B.S., M.D., BIRMINGHAM, ALA.

**A**N ATTEMPT in this instrument has been made to combine the good features of several of the currently used forceps in order to satisfy an individual desire, after a personal experience with over 2,100 forceps deliveries.

Several new ideas are incorporated, one a radical departure in forceps structure, the addition of a second lock, permitting either blade to be introduced first and so fastened.

The following are some of the advantages believed possessed by this instrument:

1. Simplicity of construction.
2. Shank of left blade carries the locks at the most desired place, fitting into the hollow of the palm when using.
3. Shank of the right blade may be locked at any part of its length, and two-thirds of the handle may be locked.
4. The hooks are unusually long to afford protection against the hand slipping; to offer more room for gripping when the hooks are used as a base for traction; to give greater safety when one blade alone is used as a "shoehorn" in rotating some part of the baby.
5. The plates between the handles are a continuation of the shank of each blade, and limit the degree beyond which the fetal head cannot be further compressed when the right blade rests on top of the left blade; enable the operator to "even" the tips of the blades when applied; afford areas for marks of identification of the blades.

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# Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

## THE AMERICAN COMMITTEE ON MATERNAL WELFARE, INC. ITS ORGANIZATION, PURPOSES AND ACTIVITIES\*

EVIDENCE of nation-wide interest in child welfare was shown by the formation in 1909 of the Association for the Study and Prevention of Infant Mortality. Although individual physicians were carrying on prenatal care in their obstetric practices, and various medical and health organizations had developed local agencies for the promotion of maternal and child welfare, interest of national scope was not in evidence until 1919. At the tenth annual meeting of the American Child Health Association in November, 1919, a resolution was adopted which led to the formation of the Joint Committee on Maternal Welfare. The American Child Health Association thus sanctioned the appointment of a committee and requested the American Gynecological Society and the American Association of Obstetricians, Gynecologists and Abdominal Surgeons each to appoint a similar committee to confer with it regarding the elaboration and development of a maternal and child welfare program in the United States.

The following year the American Gynecological Society authorized the appointment of the committee in accordance with this resolution. A collaborative committee was also appointed from the American Pediatric Society. The original committee consisted of Dr. J. Whitridge Williams, Dr. Anna E. Rude, and Dr. Merrill E. Champion representing the American Child Health Association, and Dr. George W. Kosmak, Dr. Fred J. Taussig, and Dr. Fred L. Adair representing the American Gynecological Society. Later, three members, representing the American Pediatric Society, were added to this committee: Dr. Henry L. L. Shaw, Dr. Fritz Talbot, and Dr. Walter Ramsey.

There was added to this committee, in 1921, a similar one from the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons. The personnel of this committee consisted of Dr. George Clark Mosher, Dr. Henry Schwartz, and Dr. George W. Kosmak. The Joint Committee worked out a tentative program of maternal welfare, which has been approved by the component societies. The Section on Obstetrics, Gynecology and Abdominal Surgery of the American Medical Association appointed a subcommittee to represent this Section on the Joint Committee in 1927.

The original Joint Committee recognized, in developing the plan for maternal welfare: first, the paramount importance of safeguarding the life and health of the mother, especially by decreasing in number the infections following abortion and childbirth, and by the control of the toxemias; second, the desirability of an increase in the number of fruitful pregnancies by decreasing the incidence of sterility, by reducing the number of abortions and premature births, and by attempting the prevention of stillbirths; third, the urgent need of more and better maternal care during the prenatal, natal and postnatal periods; and fourth, that concrete results in the improvement of conditions surrounding maternity and early infancy must depend largely on general application of existing knowledge and on further investigation of the many problems which contribute to morbidity and mortality of both mothers and infants.

The Committee decided that its functions were: first, the elaboration of a complete, practical scheme embodying the ideals of maternal welfare; second, the

\*Prepared by Drs. R. D. Mussey, R. L. DeNormandle, and F. L. Adair.

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The present membership consists of representatives selected from and by the following organizations: *American Child Health Association*: Dr. Robert L. DeNormandie, Dr. Fred L. Adair, and Dr. James R. McCord. *American Gynecological Society*: Dr. E. D. Plase and Dr. Philip Williams. *American Association of Obstetricians, Gynecologists and Abdominal Surgeons*: Dr. L. A. Culkins, Dr. Arthur J. Skeel, and Dr. F. H. Falls. *Section on Obstetrics and Gynecology—A. M. A.*: Dr. Fred L. Adair, Dr. R. W. Holmes, and Dr. R. D. Mussey. *American College of Surgeons*: Dr. George W. Kosmak. *Central Association of Obstetricians and Gynecologists*: Dr. James R. Reinberger. *New England Obstetrical and Gynecological Society*: Dr. Charles E. Mongan. *The American Public Health Association*: Dr. Thomas Parran, Jr. *Maternity Center Association of New York*: Miss Hurd Corbin. *Southern Medical Association*: Dr. Calvin R. Hannah. *Pacific Coast Society of Obstetrics and Gynecology*: Dr. Frank W. Lynch.

To these have been added by formal action: the Chicago Maternity Center, the Canadian Medical Association, and the Federal Children's Bureau of the United States Department of Labor.

The following officers were elected at the first meeting of the Board of Directors held on May 22, 1934: Dr. Fred L. Adair, Chairman; Dr. George W. Kosmak, Vice-chairman; Dr. James R. McCord, Secretary; and Dr. Frederick H. Falls, Treasurer. Dr. Robert L. DeNormandie and Dr. LeRoy A. Culkins were designated as members of the Executive Committee, together with the Chairman, Vice-chairman and Secretary.

The formation of State Committees on Maternal Welfare is now in progress under one of two plans of procedure: First, that some man or men may bring the matter before the State Medical Society and have them form a State Committee, which in turn would sponsor the formation of similar local committees in each of the county societies. A maternal welfare program would in this way become an official part of the activities of the various state and component county medical societies. The other plan would be for the American Committee to appoint members in a given state to serve on a local committee which would attempt to further the development of a maternal welfare program in their own state through the various local organizations under medical leadership.

The Committee believes the welfare of the infant and child is dependent largely on the welfare of the mother and that on both rests the welfare of the community. This Committee is interested in promoting such welfare by furthering the practice of safe and sane obstetrics and by stressing the importance of improved antepartum, intrapartum, postpartum and postnatal care in the interest of the mother and her offspring and the community. This end can only be obtained by the continued and increased leadership, cooperation and interest of medical men in better obstetrics. The effect of the application of teamwork in the fight against morbidity and mortality is evident in the decidedly lowered death rate in tuberculosis and many of the diseases of childhood which has resulted from campaigns led by medical men in cooperation with other agents and agencies.

Much remains to be done in the general application of our present knowledge in the prevention of those conditions which contribute to the loss of health and life in the mother. So far as the fetus is concerned, the Committee is interested in the prevention of fetal deaths, whether they occur early or late in pregnancy, as well as of those infant deaths resulting from causes arising during gestation and parturition and from preventable conditions such as infection arising in neonatal life. Its main purpose is to stimulate and aid medical men to develop and make available complete and adequate maternal care for all mothers of our country.

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Use of the Colposcope in the Diagnosis of Cervical Lesions. Dr. Carl H. Davis.  
A New Colposcope. Presented by Dr. Harry O. Maryan.  
An Instrument for Rupturing the Membranes. Presented by Dr. Irving F. Stein.

## CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF NOVEMBER 16, 1931, WITH THE CHICAGO UROLOGICAL SOCIETY

Dr. Mark T. Goldstine presented an autopsy specimen of a **Double Uterus With Two Distinct Cervical Openings and Two Cervixes** (Fig. 1). Both uteri were of normal size. The patient was five years past the menopause, had had thirteen children, and no miscarriages. There was nothing abnormal about the obstetrical history.

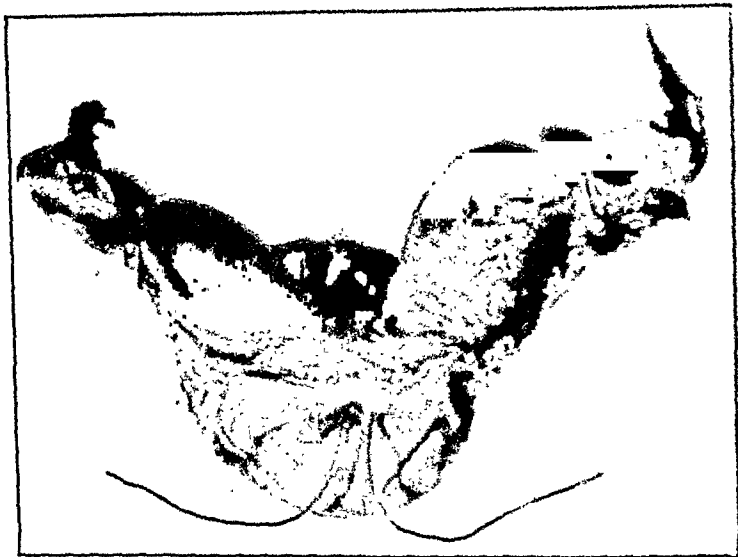


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Dr. Arthur H. Curtis read a paper on the **Postoperative Bladder in Women**, in which he reviewed briefly this problem. He believes that if a patient suffers no discomfort from inability to void, there is no imperative need for catheterization, but usually it is necessary for comfort. It is also well to catheterize for residual urine once daily, even after spontaneous voiding. Overdistention may lead to bladder paresis and require prolonged catheterization. Dr. Curtis claims that catheterization for residual urine avoids serious or persistent urinary tract infection.

Dr. Gustav Kolischer discussed **Certain Pathologic Features of the Female Urethra and Urinary Bladder**, which he felt do not receive sufficient attention. Strictures are not important but may lead to serious consequences. Primary urethral cancer may be satisfactorily treated with apposition radium therapy rather than needling. Nephritic conditions in women, more than in men, may produce vesical hematuria, from hemorrhagic patches in the fundus. It is probable that these are due to the same toxins which cause nephritic changes, and do not subside until the nephritic conditions are remedied. The effect on the bladder of radiation therapy directed to the cervix and corpus constitutes another source of vesical pathology, the cystoscopic picture being about the same as that due to syphilis. Little can be done because we have no means of influencing the nutritional disturbances. Dr. Kolischer did not believe that special filtration prevented secondary changes, as the "secondary" destructive rays are beyond our control.

These papers were discussed by Drs. N. S. Heaney, C. M. McKenna, H. O. Jones, E. L. Cornell, H. E. Schmitz, F. L. Adair, F. Falls, and V. J. O'Conner.

Use of the Colposcope in the Diagnosis of Cervical Lesions. Dr. Carl H. Davis.  
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Now then what has all this of interest to the obstetrician? We, as obstetricians, are interested in the nutrition of our patients as a whole. We are interested in conception; we are interested in the toxemias of pregnancy; we are interested in calcium and phosphorus metabolism; we are interested in resistance to infection; we are interested in full-term deliveries; we are interested in the viability and vitality of the newborn; and we are interested in a supply of breast milk adequately in quantity and quality.

It is interesting to note that our knowledge concerning vitamins, meager though it is, is going through a stage of flux as did our knowledge of the hormones a few years ago. From the literature, we gather that vitamin A is concerned with the nutrition of the epithelium, and a lack of it has long been known to produce cornification or a shift from cuboidal and columnar cells toward the squamous type. The classical illustration of its lack is the effect on the epithelial structure of the eye, with the development of the symptom complex known as xerophthalmia. A lack of vitamin A also produces a lowered state of nutrition in other epithelial structures, particularly, according to Karl Mason,<sup>4</sup> of the germinal epithelium of the testicle. There is a sloughing of the germinal cells into the tubule lumina, and a reduction in size of the lumina, occurring about the same time as xerophthalmia in experimental animals and proportional in severity. When carried to the extreme there is a greatly decreased production of spermatozoa, and the effect here is greater than in epithelium elsewhere due to its more highly organized structure and greater metabolic activity. This condition of degeneration is reversible, with recovery after from five to thirteen weeks, feeding of an optimal amount of vitamin A. The effect of a deficiency of vitamin E is more severe, affecting the nucleus of the spermatozoa. Here there is a chromolysis or liquefaction of the chromatin material and fusion of the spermatozoa into giant cells with a bead-like degeneration of the nuclei of the spermatids. The cellular removal is more complete than in avitaminosis A and is non-reversible, inasmuch as it is due to a destruction of the nuclei and there is an early discontinuation of spermatogenesis. In the female albino rat there is a resorption of the fetus from the fifth to the sixteenth day in avitaminosis E, and this is the laboratory test for the presence or absence of this vitamin. It is interesting to note why this should occur, and Mason gives a very logical explanation. He considers that vitamin E is necessary for the development of those cells which show the most rapid proliferation. The germinal cells in the male are those developing most rapidly, and the embryo in the female is the site of the most rapid proliferation. He considers the yolk sac and other hematopoietic centers the regions of the highest rate of proliferation. A deficiency of vitamin E first affects these areas with a retardation of development of the fetus, with subnormality of the yolk sac and allantois, resulting in starvation and death of the fetus with subsequent resorption.

Moore and Samuels<sup>5</sup> found the testes of rats kept on diets deficient in vitamin B to consist of seminiferous tubules, in active spermatogenesis, but that the reproductive accessories (prostate and seminal vesicles) were castrate in type. They conclude that the partial starvation induced by a lowered appetite from diets deficient in amount of sex stimulating hormone available, and leading to a lowered mice on a diet deficient in vitamin B fail to have estrus. He concludes that the anestrus is caused indirectly by its effect in producing a lack of ovarian hormone through undernutrition. Vogt<sup>7</sup> found that only 50 per cent of guinea pigs on a diet lacking in vitamin C became pregnant, and that symptoms of scurvy were more

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found that the administration of foods rich in vitamin A tends to reduce the incidence and severity of colds among school children. Hess did not find this to be true, but it was considered that the children in his study already had an adequate intake of vitamin A. Kobashitz found that the subcutaneous infection of *Staphylococcus aureus* produced more serious effects in rats deprived of vitamins A and D than in normal animals. Robertson<sup>17</sup> is of the opinion that the administration of vitamins A and D together seem on the whole to work favorably against respiratory infection. Pfannenstiel<sup>18</sup> reports the germicidal effect of the blood against *B. typhosis* was decreased with a deficiency of vitamin D, and that the specific preliminary treatment with dead staphylococci in experimental animals produced only a slight immunity to live staphylococci; but that this immunity was significantly increased by the addition of vitamins A, B, and D to the food. Clement<sup>19</sup> reported a higher immunity to diphtheria toxin in guinea pigs on a high vitamin diet than in normal animals. Otero<sup>20</sup> and coworkers found the evolution of the avian tuberculous processes seemingly accelerated in the totally depleted rats as compared with those maintained on a partially deficient or an inadequate diet. Whether the incidence of puerperal sepsis is influenced by lack of vitamins in the diet is still in controversy, with a tendency to swing toward the side of affirmative. In this connection it is interesting to follow the work of E. Mellanby and his coworkers<sup>21</sup>, who have been among the most prolific of writers on this subject. In 1924<sup>22</sup> they published an article stating that, "In an extensive study of animals brought up on a diet deficient in vitamin A, it is shown that practically all animals die from some infective or pyogenic lesions. In the control animals receiving vitamin A, these lesions are absent. These same lesions produced in animals on vitamin A deficient diets are commonly found in man." Obviously the possibility of applying this principle in man presented itself, and they selected for trial puerperal sepsis, publishing a paper on their results the following year.<sup>23</sup> They had at their command only a small series of 5 cases, but their results were of interest. In 1927 there were eight cases of puerperal sepsis with positive blood culture (*Hem. strep.*) with two recoveries on routine treatment. In 1928 there were sixteen such cases with no recoveries. During the first three months of 1929 there were five patients treated with large amounts of vitamin A (equivalent to daily intake of five ounces of cod liver oil), with five recoveries or a 100 per cent cure. Recovery was slow and blood cultures became sterile in about two weeks. Their deduction from this work was that an adequate intake of vitamin A should be of even greater value as a prophylactic against the incidence of puerperal sepsis. Two years later<sup>24</sup> following this line of thought, they published another paper showing the results in 550 women in the antenatal clinic of Sheffield University Hospital. Alternate cases were given an extra supply of vitamins A and D during the later weeks of pregnancy. The morbidity as measured by the British standard unit of morbidity following childbirth was four times as frequent (4.7 per cent) as it was in those patients who received vitamins (1.1 per cent).

Sherman and Smith<sup>24</sup> in commenting upon this work suggested that "on account of these promising results vitamin A should be given very extensive clinical tests in this connection."

Torrence<sup>25, 26</sup> has since then published a series of experiments, showing first, that 30 per cent more pregnant guinea pigs succumbed to intraperitoneal injections of hemolytic streptococcus than those nonpregnant. Second, that the vitamin A reserve in the livers of rabbits, which had recently borne and nursed young, was found to be lower than in livers of virgin animals. In other words, pregnancy and lactation lowered the reserve of vitamin A stored in the liver, and resistance to hemolytic streptococcus was less during pregnancy. In any case, there is a pro-

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Third, there is an impairment of assimilative power, which with a bowel content already inefficiently digested would again contribute to malnutrition.

Fourth, due to the decreased state of nutrition of the mucous membrane of the intestinal tract caused by a lack of both vitamins A and B, there is an impairment of the protective reaction against infection caused by pathogenic saprophytes and ingested organisms.

In addition to this Schrader<sup>25</sup> has shown an impairment of carbohydrate metabolism, with a lack of vitamin B in the diet, and Lohb<sup>26</sup> and associates have been able to substitute B for insulin, to a certain extent, in the treatment of diabetes. With an impairment of efficient carbohydrate metabolism with a fractional avitaminosis B, the nutrition of the patient would be further restricted. Inasmuch as vitamin B is necessary for optimal nutrition, it should deserve particular consideration during pregnancy.

Obesity is considered by DeLee<sup>27</sup> as a complication of pregnancy, influencing the progress of labor and making operative procedures more difficult.

Wilder<sup>28</sup> states that excessive eating by some persons may be explained by an unconscious effort to secure adequate vitamins. This eating in excess of the demands for the production of energy, provides a surplus which in many people is stored in the fat depots.

In a certain small percentage (about 3 per cent according to some authorities),<sup>29</sup> the endocrines play a part, but endocrine obesity is undoubtedly always complicated by the nutritional type. When these people are given a vitamin ration from natural sources and in clinical balance, they can undertake a low calory diet of, say 1,200 per day, with a minimum of self-denial in the way of hunger and without the development of the usual deficiency symptoms met with, in the use of the ordinary starvation diets, and still with a steady and continuous weight loss of from three to five pounds a week. They show an increased sense of well-being greater than can be explained by the weight loss alone, and in pregnancy where obesity of the nutritional type exists, a weight loss may be obtained not only without endangering mother and child but with actual benefit due to the increased intake of vitamins.

#### SUMMARY AND CONCLUSIONS

1. Notwithstanding that the average American diet is fairly well balanced, there is still a relative deficiency of vitamins.
2. A lack of vitamins has the effect of inhibiting normal conception, and should be included in the consideration of the subject of sterility.
3. Premature deliveries and stillbirths may be favorably influenced in certain cases by an adequate vitamin intake.
4. Infections during pregnancy and the puerperium may be favorably influenced or prevented by a diet adequate in vitamins.

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## Selected Abstracts

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### Pregnancy Complicated by Various Diseases

Vignes, H.: Lumbar Neuralgias of Pregnancy, *Bull. Soc. d'obst. de la gynéc.*, p. 37, 1934.

Many years ago the author investigated a group of pregnant women who had symptoms, especially neuralgic pains, which we have come to attribute to vitaminosis. He, therefore, recently undertook a study to determine whether or not these symptoms were due to lack of vitamin B. During the past two years Vignes has prescribed fresh beer for all pregnant women who complained of neuralgic pains. Success with this therapy has been immediate, constant relief being observed within three or four days at the most.

J. P. GERSHBERG.

Vandal, D. T.: Polyneuritis of Pregnancy: A Vitamin Deficiency Disorder, *J. Missouri M. A.* 30: 407, 1933.

Polyneuritis of pregnancy is similar to beriberi, both of which result from a lack of proper vitamins in the diet. Correction of the dietary deficiency is obtained by supplying the vitamin B complex. When pernicious vomiting of pregnancy occurs, vitamin B should be used as a prophylactic.

J. THORNWELL WITHERSPOON.

Maxwell, J. Preston: Vitamin Deficiency in the Antenatal Period, Its Effects on Mother and Infant, *J. Obst. & Gynec. Brit. Emp.* 39: 764, 1932.

The author offers an extremely interesting and concise account of the various vitamins and their probable rôle played during pregnancy. A report is given of a case of antenatal vitamin A deficiency, resulting in antenatal keratomalacia. Also "a case which was almost certainly a case of antenatal vitamin C deficiency," resulting in pyrexia and swelling of the right knee on the seventh day of life, is presented. Six cases, three of them previously reported, of fetal rickets are discussed in detail. Three of these six babies also had hemorrhagic disease at birth, and the author points out that though this disease occurs in about one birth in two thousand, "here we have three out of six cases of fetal rickets suffering from the disease." He concludes with the assertion that "probably the vitamins are more important during pregnancy than at any other period of the life history of a woman."

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WILLIAM F. MENGERT.

Strauss, M. B., and Castle, W. B.: The Etiologic Relationship of Gastric Secretory Defects and Dietary Deficiencies to the Hypochromic and Macrocytic (Pernicious) Anemias of Pregnancy and the Treatment of These Conditions, *Am. J. M. Sc.* 185: 539, 1933.

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scattered areas the sarcoplasm was being absorbed and the sarcotomus with pyknotic nuclei remained. The blood vessels appeared normal; there was no perivascular infiltration.

W. B. STROM.

**Bolaffio, M.: Pernicious Anemia of Pregnancy, Arch. f. Gynäk. 151: 165, 1932.**

The author stresses the apparent scarcity of reports of pernicious anemia in the German literature and contrasts this with the frequency with which this condition is met in Italy. He then reports in detail on 37 cases which he has followed. In every instance the red blood cell count was less than one million with an increased color index.

A lability of the blood may develop in pregnancy which changes the chemistry and composition of the blood plasma. This leads to oligocythemia and oligochromia. These are probably due to a constitutional predisposition of the bone marrow and particularly to an inertia of gastric secretion which should normally stimulate blood formation. Disintegration of the blood is increased due to the placental metabolism.

The end-result of these processes is the pernicious anemia of pregnancy, there being a definite deficiency of the blood-stimulating hormone. It is therefore identical with cryptogenic pernicious anemia and differs only in its etiology. Liver therapy is specific for both types, and will, in the pregnancy type, permit the pregnancy to go to term. Transfusions are of value in the severe forms. Interruption of pregnancy is rarely indicated but may be necessary with acute exacerbations which do not respond. Recurrences during subsequent pregnancies are so rare that sterilization is never indicated.

RALPH A. REIS.

**Fauvet, E.: The Leucocytosis of Pregnancy and Labor, Monatschr. f. Geburtsh. u. Gynäk. 90: 221, 1932.**

Fauvet emphasizes that the leucocytosis of pregnancy and that of labor are distinct processes. The former is due to the generalized growth activity of pregnancy but the ultimate cause is unknown. The leucocytosis of labor, however, is due to the activity of the uterus and is of prophylactic value.

J. P. GREENHILL.

**Terada, E.: Ectopic Chorionepithelioma Malignum Complicated by Pregnancy, Japanese J. Obst. & Gynec. 16: 121, 1933.**

A case of ectopic chorionepithelioma observed during pregnancy is reported. He claims that the only two similar cases have been reported, by Walthard, and Shiga. In both of them the malignant tumor was in the vaginal wall. Terada believes that in his case the chorionepithelioma was primary in the bladder.

J. P. GREENHILL.

**Kuhnel, P.: Death From Salvarsan Treatment in Pregnancy, Acta obst. et gynec. Scandinav. 13: 29, 1933.**

Twenty cases of fatal salvarsan intoxication were gathered from the literature by the author. To this material are added 3 cases from Denmark not published before.

The latter half of pregnancy involves a far greater risk of fatal salvarsan intoxication than do the first months. In most of these cases the symptoms of intoxication set in after the second or third injection of salvarsan. In 15 of 19 cases

scattered areas the sarcoplasm was being absorbed and the sarcolemma with pyknotic nuclei remained. The blood vessels appeared normal; there was no perivascular infiltration.

W. B. SERBIN.

**Bolaffio, M.:** Pernicious Anemia of Pregnancy, *Arch. f. Gynäk.* 151: 465, 1932.

The author stresses the apparent scarcity of reports of pernicious anemia in the German literature and contrasts this with the frequency with which this condition is met in Italy. He then reports in detail on 37 cases which he has followed. In every instance the red blood cell count was less than one million with an increased color index.

A lability of the blood may develop in pregnancy which changes the chemistry and composition of the blood plasma. This leads to oligocythemia and oligochromia. These are probably due to a constitutional predisposition of the bone marrow and particularly to an inertia of gastric incretion which should normally stimulate blood formation. Disintegration of the blood is increased due to the placental metabolism.

The end-result of these processes is the pernicious anemia of pregnancy, there being a definite deficiency of the blood-stimulating hormone. It is therefore identical with cryptogenic pernicious anemia and differs only in its etiology. Liver therapy is specific for both types, and will, in the pregnancy type, permit the pregnancy to go to term. Transfusions are of value in the severe forms. Interruption of pregnancy is rarely indicated but may be necessary with acute exacerbations which do not respond. Recurrences during subsequent pregnancies are so rare that sterilization is never indicated.

RALPH A. REIS.

**Fauvet, E.:** The Leucocytosis of Pregnancy and Labor, *Monatschr. f. Geburtsh. u. Gynäk.* 90: 221, 1932.

Fauvet emphasizes that the leucocytosis of pregnancy and that of labor are distinct processes. The former is due to the generalized growth activity of pregnancy but the ultimate cause is unknown. The leucocytosis of labor, however, is due to the activity of the uterus and is of prophylactic value.

J. P. GREENHILL.

**Terada, E.:** Ectopic Chorionepithelioma Malignum Complicated by Pregnancy, *Japanese J. Obst. & Gynec.* 16: 121, 1933.

A case of ectopic chorionepithelioma observed during pregnancy is reported. He claims that the only two similar cases have been reported, by Walthard, and Shiga. In both of them the malignant tumor was in the vaginal wall. Terada believes that in his case the chorionepithelioma was primary in the bladder.

J. P. GREENHILL.

**Kuhnel, P.:** Death From Salvarsan Treatment in Pregnancy, *Acta obst. et gynec. Scandinav.* 13: 29, 1933.

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Applications for Group A candidates must be received not later than May 1, 1935.

The annual informal dinner and general conference of Diplomates attending the American Medical Association convention will be held at the Traymore Hotel, Atlantic City, Wednesday, June 12 at 7 p.m. At this dinner the successful candidates from the examinations of the two preceding days will be presented in person, and short addresses will be made by several members of the Board.

For further information, booklets, and application blanks apply to the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, 16 Pennsylvania.

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Meetings are held the first Monday of February, April, June, October and December. The officers are Dr. T. B. Carroll, President; Dr. Paul Titus, Vice-President; Dr. T. K. Reeves, Secretary-Treasurer; Dr. S. A. Chalfant and Dr. J. A. Trumpeter, Executive Council.

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The estrogenic substances used in our cases were amniotin\* and the benzoic acid ester of dihydroestrin (progynon B). The solvent for both is oil. The concentration of hormone is as follows:

Amniotin 1 c.c. = 1,000 R.U. (5,000 M.U.)

Progynon B. 1 c.c. = 10,000 R.U. (50,000 M.U.)

The two substances are not identical chemically. Amniotin is derived from the amniotic fluid of cattle and is chemically a ketohydroxyestrin (Fig. 1). Progynon B is derived from mares' urine first as ketohydroxyestrin. In an important experiment Schwenk and Hildebrandt (1933) found that by reducing the keto group ( $\text{--C--O}$ ) to a hydroxyl group (significant groups noted by circles), so as to form dihydroestrin (Fig. 3), the estrogenic activity of the hormone is "stepped up" tremendously. Because of the protracted excretion of the benzoic ester of estrin, first observed by Butenandt (1931), a benzoic acid ester of the dihydroestrin was prepared by coupling the phenolic hydroxyl (on ring A) with benzoic acid (Fig. 4). The esterification of the dihydroestrin reduces its activity but prolongs its physiologic effect,† because the ester is more slowly broken up by the body. As the dihydroestrin and its esters are much more soluble in oil than estrin itself, the use of these com-

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†When 1 M.U. of estrin is injected, full estrus is caused for only a day, and diestrus (interval between two estrus cycles) is restored within four days, the injection of 1 M.U. of the benzoate is followed by an estrus lasting for about five days, and complete diestrus is restored in some thirteen days after the injection. The clinical significance of this effect is apparent.

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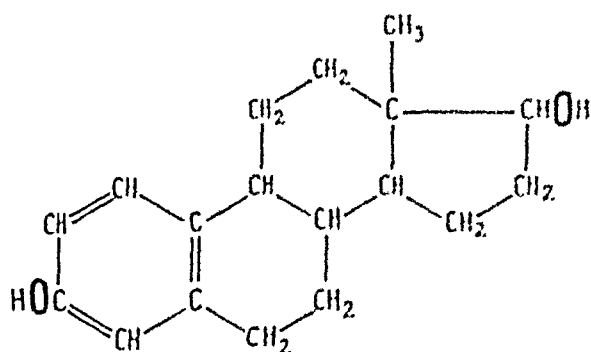
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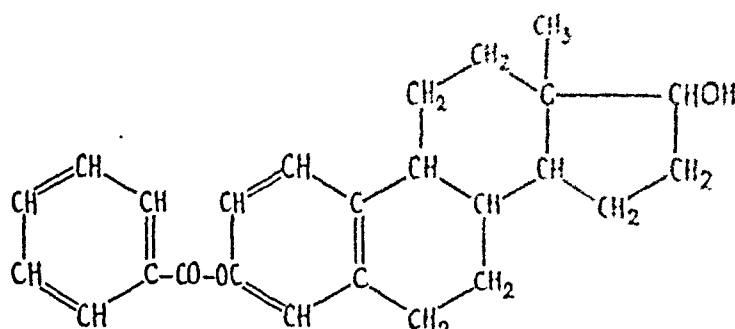
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Dihydroestrin  $\text{C}_{18}\text{H}_{26}\text{O}_2$   
1 gm. = 25,000,000 M.U. or  
= 5,000,000 R.U.

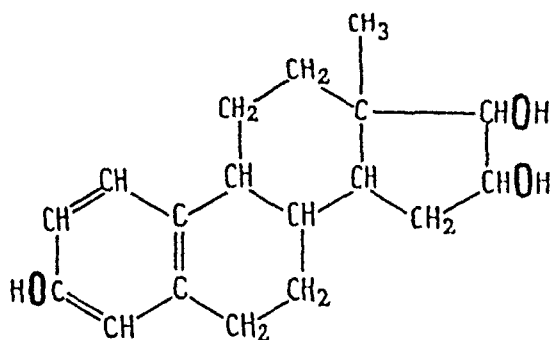
Fig. 3.



Benzene Acid

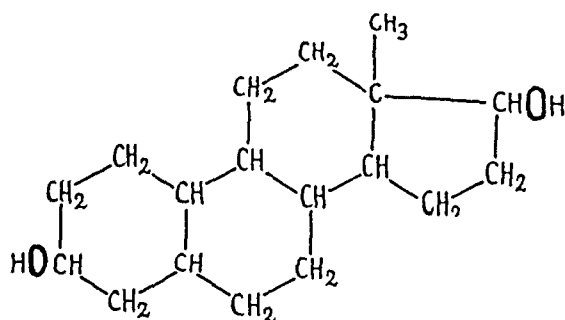
Fig. 4.

Benzene acid ester of  
dihydro-estrin or  
progynon - B.  
1 gm. = 12,500,000  
M.U. or  
= 2,500,000  
R.U.



Thecdol or trihydroxyestrin.  
1 gm. = 15,000 - 40,000 R.U.  
or  
75,000 - 200,000 M.U.

Fig. 5.

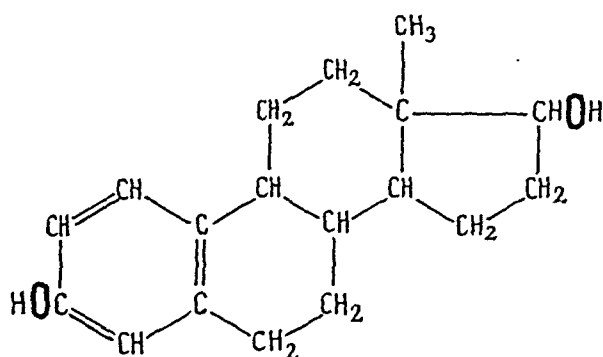


Hydrogenation product of estrin.  
3,17 dihydroxyestrane

Fig. 6.

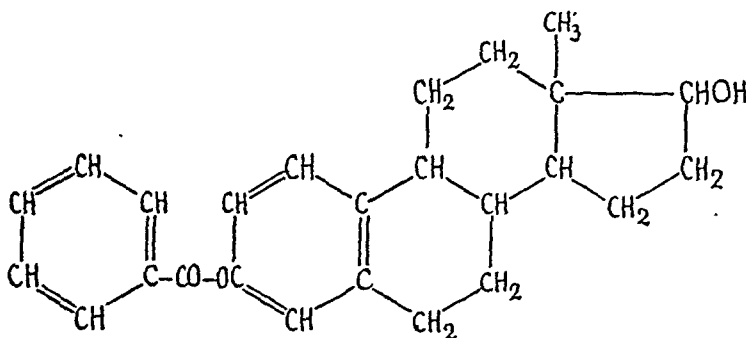
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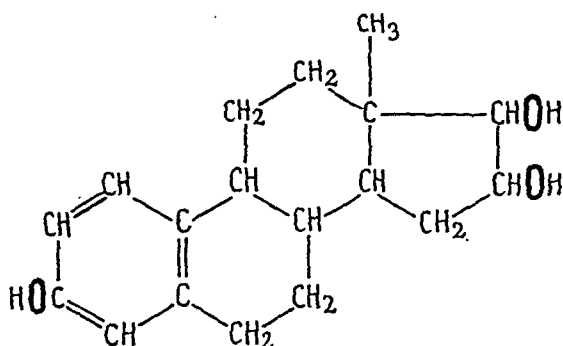
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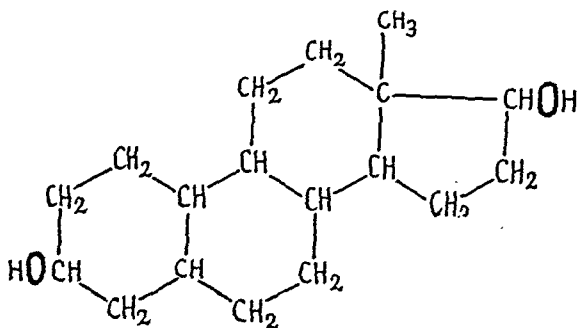
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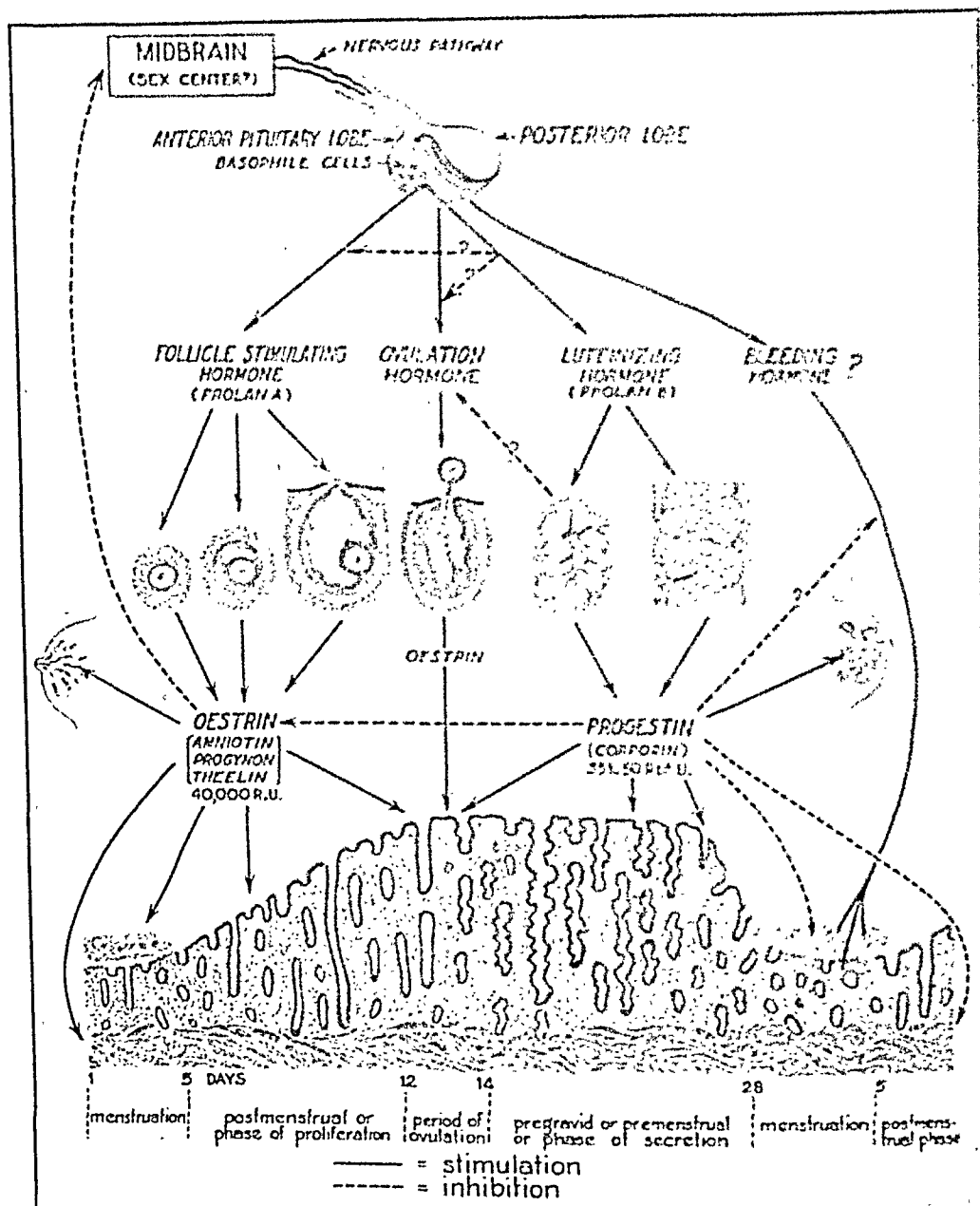


Fig. 9.—Represents the sex hormones involved in the menstrual cycle and their interrelationships. The ovarian hormones are represented quantitatively, the progesterin in terms of the Clauberg Unit. A sex center is postulated mainly on the work of Teel and Cushing (1930) and Hohlweg and Junkmann (1933). The relation of the breasts to the ovarian hormones is also shown.

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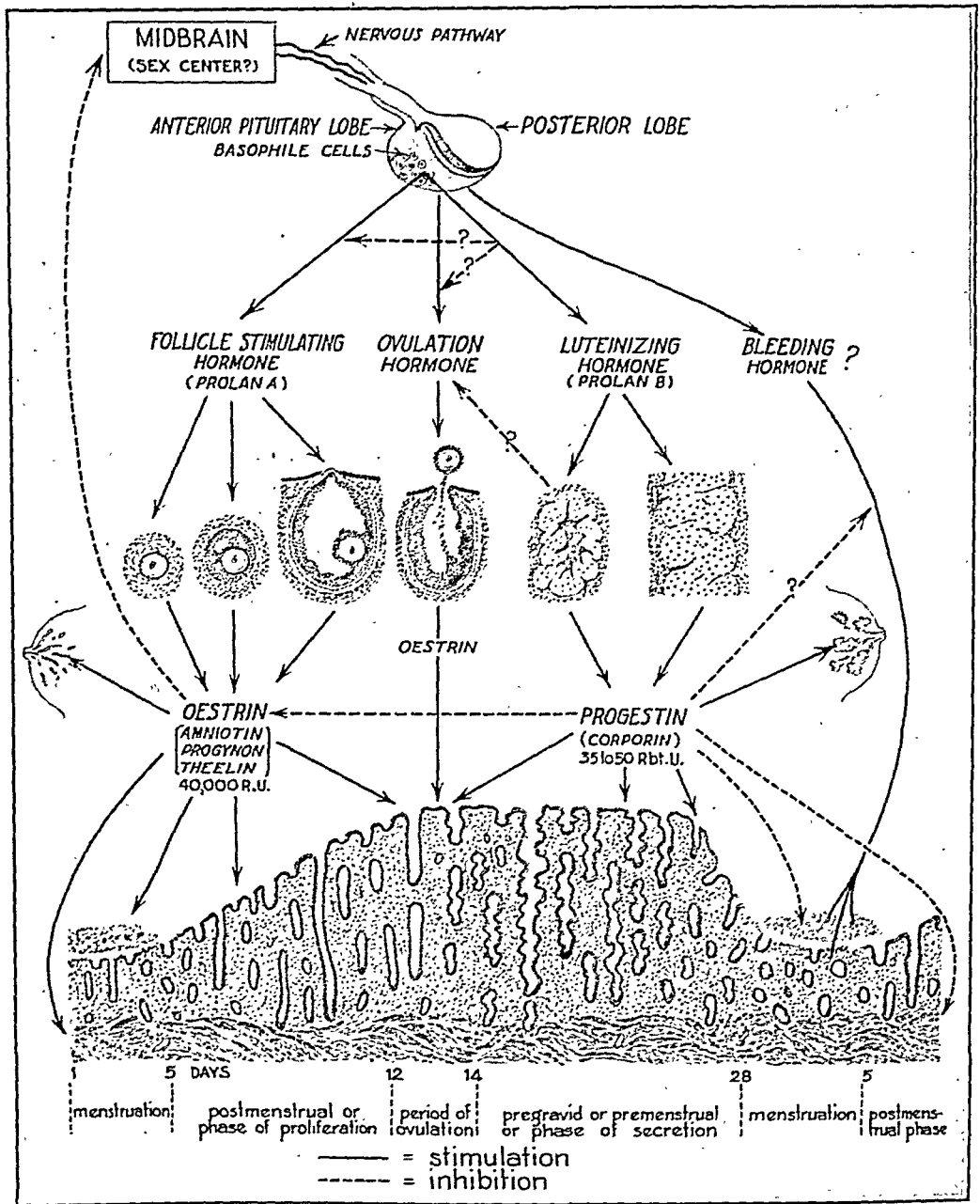


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The development of the mammary gland and its cyclical changes during menstruation depend upon the hormones produced by the ovary and the anterior lobe of the pituitary. Estrin stimulates the growth of the duct system (Turner, etc., 1932). Corpus luteum hormone stimulates the alveolar apparatus. The breast undergoes cyclical changes during the menstrual cycle. Grueter and Stricker (1929) showed that injections of anterior pituitary extracts into ovariectomized rabbits produced development of the mammary gland and lactation. They believed that previous corpus luteum activity was essential for this growth. Corner (1930) showed that anterior pituitary extracts alone were sufficient to produce mammary growth. Only estrogenic substances were used in our cases.

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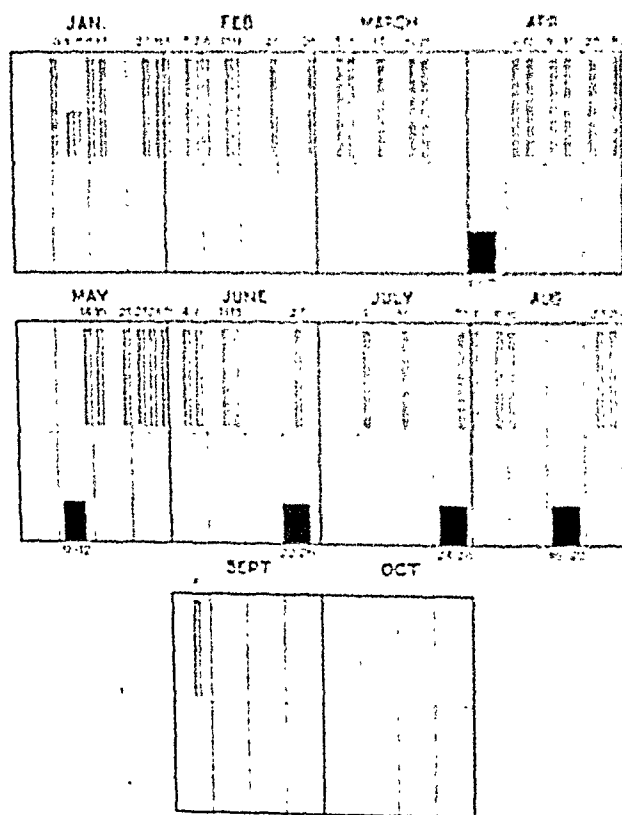


Fig. 11.—L. L. B., aged twenty-two years. Primary amenorrhea. General infantilism. Hypodevelopment of secondary sex characteristics (Group I). Estrin, negative; follicle-stimulating hormone, positive; basal metabolic rate minus 27 per cent 184,000 R.U. of progynon B required to bring on first period. Solid column denotes duration and intensity of flow. Each barred column denotes 10,000 R.U. of estrogenic hormone; shorter columns correspondingly less.

ful. The growth was confined chiefly to the region of the areolae and nipples (duct system). Vaginal secretion was the next to appear accompanied by enlargement of the labia and apparent widening of the vagina. This was soon followed by bleeding from the uterus, which in the beginning showed little if any increase in size. After several months of treatment the uterus became considerably enlarged. The quantity of progynon B and amniotin necessary to produce the above effects varied considerably. In general, it required about 50,000 R.U. to produce appreciable growth of the breasts; 100,000 R.U. to bring about the first period, and about 40,000 R.U. to bring about subsequent periods.

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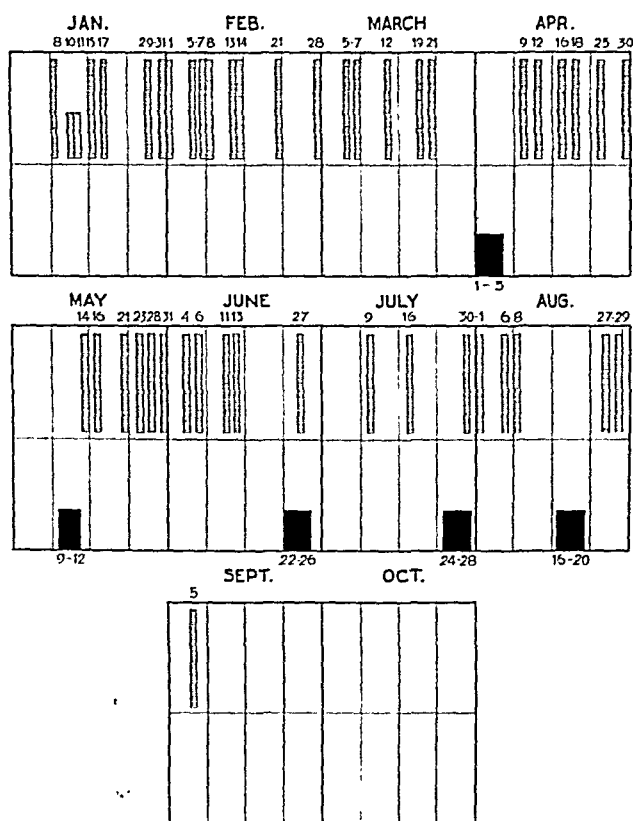


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Each patient was given 100,000 R.U. of progynon B over a period of two months. In one case, there has been definite enlargement of the uterine anlage from a vague thickening in the broad ligament to a nodule the size of a hazelnut. The other case has shown no growth and treatment has been discontinued. The interesting point here is the growth in extrauterine life of an anlage which had previously failed to develop during intrauterine existence.

Group II b (partial failure of müllerian duct development) was composed of four patients. They had infantile uteri but well-developed breasts and external genitalia.

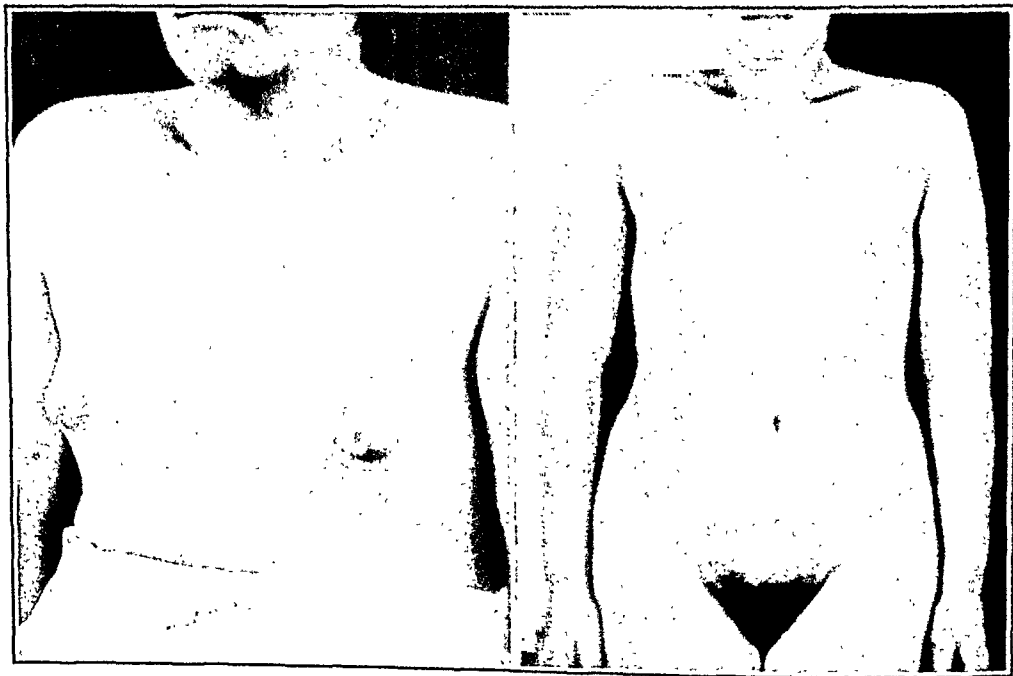


Fig. 13.—Growth of breasts from 100,000 R.U. progynon — B. R. P., aged nineteen years. Primary amenorrhea Group I, marked hypodevelopment of all secondary sex characteristics. Has had 5 successive periods under treatment. Distinct change in psychic outlook.

Hormone determinations of the urine showed neither estrin nor prolan but the development of breasts, external genitalia, and female body contour was indicative of some ovarian function.

Under treatment with progynon B, one patient has had 4 successive periods, and three one period each. The quantity of flow was in general greater than in Group I. The possibility of continued menstruation without further treatment exists in these patients (unlike Group I), because their ovaries are functioning. It will probably be necessary to continue the administration of progynon B until the uterus has attained adequate development.

Endometrium removed prior to the onset of bleeding from one patient showed secretory changes. Since no corpus luteum hormone was administered, the progestrin was derived from the patient's ovaries.

case, but 8 R.U. of estrin was found in one patient and no estrin in the other. The absence of estrin in the latter case does not mean complete cessation of ovarian function; the presence of well-developed breasts and external genitalia and the absence of F.S.H. indicate some ovarian activity.

Each patient was given 100,000 R.U. of progynon B over a period of two months. In one case, there has been definite enlargement of the uterine anlage from a vague thickening in the broad ligament to a nodule the size of a hazelnut. The other case has shown no growth and treatment has been discontinued. The interesting point here is the growth in extrauterine life of an anlage which had previously failed to develop during intrauterine existence.

Group II b (partial failure of müllerian duct development) was composed of four patients. They had infantile uteri but well-developed breasts and external genitalia.

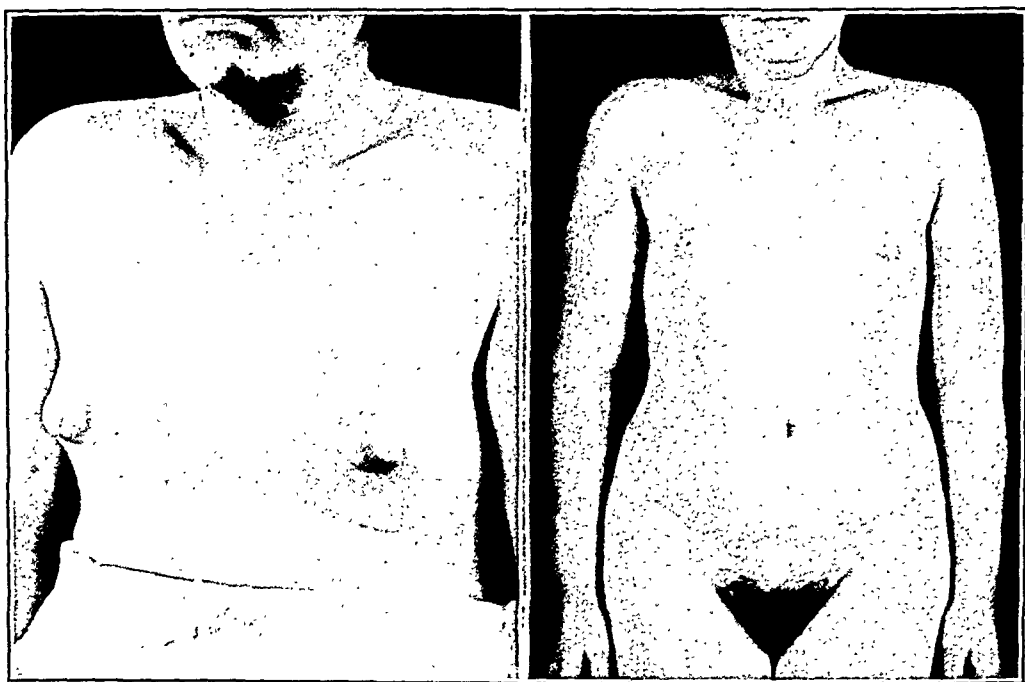


Fig. 13.—Growth of breasts from 100,000 R.U. progynon — B. R. P., aged nineteen years. Primary amenorrhea Group I, marked hypodevelopment of all secondary sex characteristics. Has had 5 successive periods under treatment. Distinct change in psychic outlook.

Hormone determinations of the urine showed neither estrin nor prolan but the development of breasts, external genitalia, and female body contour was indicative of some ovarian function.

Under treatment with progynon B, one patient has had 4 successive periods, and three one period each. The quantity of flow was in general greater than in Group I. The possibility of continued menstruation without further treatment exists in these patients (unlike Group I), because their ovaries are functioning. It will probably be necessary to continue the administration of progynon B until the uterus has attained adequate development.

Endometrium removed prior to the onset of bleeding from one patient showed secretory changes. Since no corpus luteum hormone was administered, the progestrin was derived from the patient's ovaries.

TABLE II. SECONDARY AMENORRHEA

NUMBER	AGE	DURATION OF AMENORRHEA	OBESITY	HIRSUTISM	GENITAL HYPOPLASIA	ESTRIN R.U. LATER	A.P.H.	B.M.R.	NUMBER OF SUCCESSIVE PERIODS	MENSTRUATION WHEN TREATMENT STOPPED
401043	21	6 yr.	+	-	Moderate	4	0	Not done	4	No
76814	21	2½ yr.	+	-	External and internal	0	0	-14	3	Failed to return
365777	33	8 yr.	+	-	Ext. and internal (marked)	(Not done)	(Not done)	-10	3	Failed to return
256512	25	1½ yr.	+	-	Ext. and internal	0	0	+11 -1	4	Failed to return
338313	32	5 yr.	+	+	Internal	0	0	-18	2 (Insufficient treatment)	No
409885	23	1 yr.	-	-	Ext. and internal	0	0	-10	3	No
386304	19	3 yr.	-	-	Internal	1	0	-18	6	Treatment still in progress
358137	32	1½ yr.	-	-	Internal	0	0	Not done	2	Treatment still in progress
28633E	17	1½ yr.	---	-	Ext. and internal	(Not done)	(Not done)	Not done	0 (94,000 R.F.)	3 successive periods with follicles, none since
300879	36	2 yr.	-	-	None	(Not done)	(Not done)	Not done	2	No
385081	35	1 yr.	-	-	External	0	0	-4	3	1 (Phase far) all scanty
96627	32	Every 3 mo.	-	-	External	4	0	-4	4	No
E. G.	29	3-22 mo.	+	+	Internal (mild)	8	0	-3	6	2

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10. The endometrium which has been built up to the proliferative phase by an external supply of estrin may be converted to the pregravid phase by the patient's own corpus luteum.

We are indebted to Professor Benjamin B. Watson for constant encouragement and advice, and for his placing the large material of the Rhode Hospital for Women and the Vanderbilt Clinic at our disposal. We also wish to thank Drs. John C. Kitzes, Thomas J. Parks, Charlotte H. Phillips and Hans Wechsler for their kind cooperation and help.

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to the sixteenth day of the cycle, external bleeding from the interval type of endometrium results in three to five days (Allen, 1927). Even earlier ablation will cause bleeding (Van Wageningen and Aberle, 1931). Aspiration of several large follicles in an adult monkey causes bleeding in six days (Allen, 1926). If a monkey is spayed and estrin injections begun at once bleeding will not occur, or if treatment is delayed for two or three days bleeding may occur but is shorter than it would have been had no treatment been given, even if treatment is delayed to the first day of bleeding. When the endometrium of spayed monkeys has been built up by estrin injections to the interval type, stopping the treatment results in bleeding in five to seven days, and if the level of the dosage is lowered three or four days before the last treatment, bleeding occurs earlier than when a full dosage had been maintained throughout (Allen, 1926). If the lower level of estrin dosage is continued, bleeding also occurs (experiments of Hixson et al., quoted by Corner, 1933\*).

All the above observations on ovarian extirpation followed by bleeding were made on adult or subadult animals. In immature animals in which estrin secretion, as shown by the sex skin, has not yet reached the pubertal level, ovariectomy does not induce bleeding, as shown by Allen in 1928 with 2,500 gm. animals. In frankly immature animals or those nearing maturity in our series (3 of 2,000 gm. body weight, 1 of 3,000 gm., and 1 of 2,200 gm.) unilateral ovariectomy did not result in bleeding by the sixth or by the eighteenth day in 2 animals of 2,500 gm.

It may be clearly accepted that estrin withdrawal in animals whose endometrium had been stimulated by this hormone results in bleeding. It must be recognized, however, that none of these experiments threw light on the question of whether estrin withdrawal will produce menstruation or not if the endometrium has undergone a progestational proliferation, and entered the gravid stage attained just prior to the onset of menstruation in the characteristic complete human cycle.

*The Anterior Pituitary and Menstruation—the Direct Stimulation Theory of Hartman et al.*—The pronouncement of Hartman, Firor and Geiling (1930) that menstrual bleeding was a direct effect of a principle of the anterior pituitary, and, therefore, not referable to a withdrawal of a hormone, stimulated investigation. In this work Hartman et al. used extracts both of the anterior pituitary (A.P.) and of pregnancy urine and were under the impression, current at that time, that the gonadotropic principle in pregnancy urine was elaborated by the anterior pituitary and therefore that its injection constituted true pituitary treatment.

1. *The Effect of Anterior Pituitary Extracts.*—An analysis of the data of Hartman and his associates (Protocols 31, 82, 85, 86, and 91) reveals the fact that in all cases in which true anterior pituitary extracts were used, bleeding occurred after the cessation of treatment and therefore lend no support to the idea that a direct stimulus of the endometrium by the pituitary injections induced menstruation. Since the treatments were performed on nonovariectomized monkeys, they are referable to the cessation in the stimulation of the ovary and estrin production concomitant with cessation of the anterior pituitary injections. Saiki (1932), who injected special sheep anterior pituitary extracts and found that bleeding followed the cessation of treatment, interpreted his experiments in this way. He noted a reddening of the sex skin during the injections and when treatment was stopped, the sex skin became pale, a response which is an excellent index of estrin production. When ovariectomized animals were used, the anterior pituitary injection caused no reddening of the sex skin, and cessation of treatment was not followed by bleeding. Thus the data of Hartman and of Saiki are uniform. The latter, however, contrary to Hartman, referred his findings to a stimulation of the ovary by the anterior pitu-

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It must be stated, however, that our observations reported above, and those to be presented later in this paper differ in one respect from some of those of Hartman, in which the animals were reported to have been hypophysectomized. We are thoroughly aware that complete hypophysectomy may modify the response to pregnancy urine injections or to any other hormone affecting the genital system.

It seems clear that at least one of the causative factors in the production of uterine bleeding with pregnancy urine injections in normal animals is a lowering of the estrin level induced by the repressing action of the injections on the ovaries. As in the case of estrin injections or ovariectomies, however, none of these cases reveals the causative factor of menstruation, when a progestational proliferation has taken place as in the complete ovulatory cycle. In order to determine the factor responsible for menstruation under such a condition, experiments with a pro gravid endometrium are necessary. Such experiments will be described in the two following sections.

#### EXPERIMENTAL DATA

*Inhibition of Expected Uterine Bleeding by Progesterone.*—Data from this and other laboratories summarized in the preceding paragraphs show that estrin withdrawal will cause uterine bleeding in adult or subadult monkeys whose endometrium has not undergone a progestational proliferation. As there stated, these data do not show, however, for the complete ovulatory cycle that estrin withdrawal is the primary or even an important factor in the induction of menstruation for in the ovulatory cycle, presumably the usual type in the human being, a pro gravid endometrium develops. To aid in determining the important immediate factor, estrin or progesterone withdrawal, operating in the complete cycle in the induction of menstruation, experiments were planned to answer the following questions: (1) Will the administration of progesterone following high estrin secretion or administration and its subsequent withdrawal prevent menstruation? (2) If so, will continued administration of progesterone continue to prevent menstruation? (3) Will the administration of estrin consequent to progesterone injections (with the development of a pro gravid endometrium) prevent menstruation if the injection of progesterone is stopped?

The experiments outlined under (1) and (2) above will be discussed in this section.

In the first series of these experiments, adult or subadult monkeys were treated with the follicle-stimulating fraction of the anterior pituitary which, when given subcutaneously, causes no luteinization. There is no advantage in the use of the extract of the anterior lobe over the direct administration of estrin, except that a more uniform and constant liberation of estrin is achieved. No difference has been noted in the structure of the endometrium between these two methods of treatment. With either method a good interval endometrium is developed. The addition of

dition to the animals reported here, we have in other animals demonstrated the adequacy of the progestational proliferation by the mechanical stimulation of a decidual response, comparable to that reported in early pregnancy by Streeter and Hartman.

#### PROTOCOLS

Monkey 71 ♀.—4,350 gm., uterus 10 mm. broad on digital palpation. A.P. (aqueous fraction of pyridine extract of dried sheep anterior pituitary) 40 c.c. (13.3 gm. dry powder) twice daily 10 days, subcutaneously. Last 4 days of A.P. treatment 19 c.c. Theelin given concurrently (50 R.U. per c.c.). Progestin instituted day after last A.P.-theelin treatment and continued for 11 days. Daily dose 45 gm. equivalent, fresh hog corpora lutea. No bleeding for the entire period. Autopsy on twelfth day after cessation of theelin.

Monkey 79 ♀.—3,350 gm. A.P. 30 c.c. (10 gm.) for 10 days S.C. + 8 days (21 c.c. 7 gm.) intravenously. Theelin on last 3 days (total 9 c.c. 450 units). Both ovaries removed. Uterus 11.4 by 9 mm. First injection of progestin on day of operation. Progestin for 10 days (1 c.c. = 38 gm., total 541 gm. fresh hog corpora lutea). Tolerated progestin badly, blood in vaginal lavage, on fourth day after cessation of progestin treatment. Autopsy.

Monkey 82 ♀.—3,700 gm. A.P. 14 days (10 gm.), last four days 16 c.c. (800 units) theelin. Progestin on day following last injection. Theelin continued for 15 days. Total 1,260 gm. fresh hog corpora lutea. No blood even on vaginal lavage. On last, fifteenth day, of progestin treatment uterus measured 16.1 by 12.3 mm. Sample of uterus removed, next day slight blood in vaginal lavage. Good external flow on fifth day after last progestin treatment. Autopsy on second day of bleeding, uterus 37.8 cervix-fundus 15.2 infratubal width, 14 greatest depth.

Monkey 89 ♀.—4,450 gm. A.P. 13 days; last three days of this course 14 c.c. (700 units) theelin. Day following last injections both ovaries removed. Uterus 18.0 by 14.7 mm. Progestin given on day of operation and for 28 days. Total 1,781 gm. fresh hog corpora lutea (63.6 gm. daily); no vaginal blood during the course of treatment. Slight vaginal bleeding on fifth day after last injection. Profuse flow with large clots on sixth day. Autopsy second day of bleeding. Uterus 35.4 by 19.8 by 13.7 mm.

It is, thus, conclusively demonstrated that the administration of progestin will prevent bleeding after a complete withdrawal of estrin. Furthermore, after a pro gravid type of endometrium has been produced by the progestin injections, a condition identical with the complete ovulatory cycle, the continued injection of progestin will continue to prevent menstruation, a flow not occurring until four or six days after the progestin injections are finally stopped.

*The Failure of Estrin to Prevent Bleeding From a Progestational Endometrium.*—The data presented above demonstrate that experimentally the usual bleeding of estrin privera may be prevented for as long as a twenty-eight-day period of progestin administration. This conforms to the usual clinical concept of menstruation that cyclic bleeding most commonly occurs after the breakdown of a corpus of ovulation in the non gravid cycle.

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Monkey 82 ♀.—3,700 gm. A.P. 14 days (40 gm.), last four days 16 c.c. (800 units) theelin. Progesterin on day following last injection. Theelin continued for 15 days. Total 1,260 gm. fresh hog corpora lutea. No blood even on vaginal lavage. On last, fifteenth day, of progesterin treatment uterus measured 16.1 by 12.3 mm. Sample of uterus removed, next day slight blood in vaginal lavage. Good external flow on fifth day after last progesterin treatment. Autopsy on second day of bleeding, uterus 37.8 cervix-fundus 15.2 infratubal width, 14 greatest depth.

Monkey 89 ♀.—4,450 gm. A.P. 13 days; last three days of this course 14 c.c. (700 units) theelin. Day following last injections both ovaries removed. Uterus 18.0 by 14.7 mm. Progesterin given on day of operation and for 28 days. Total 1,781 gm. fresh hog corpora lutea (63.6 gm. daily); no vaginal blood during the course of treatment. Slight vaginal bleeding on fifth day after last injection. Profuse flow with large clots on sixth day. Autopsy second day of bleeding. Uterus 35.4 by 19.8 by 13.7 mm.

It is, thus, conclusively demonstrated that the administration of progesterin will prevent bleeding after a complete withdrawal of estrin. Furthermore, after a pro gravid type of endometrium has been produced by the progesterin injections, a condition identical with the complete ovulatory cycle, the continued injection of progesterin will continue to prevent menstruation, a flow not occurring until four or six days after the progesterin injections are finally stopped.

*The Failure of Estrin to Prevent Bleeding From a Progestational Endometrium.*—The data presented above demonstrate that experimentally the usual bleeding of estrin privia may be prevented for as long as a twenty-eight-day period of progesterin administration. This conforms to the usual clinical concept of menstruation that cyclic bleeding most commonly occurs after the breakdown of a corpus of ovulation in the non gravid cycle.

It now remained to determine whether or not the injection of estrin would prevent menstruation if commenced at the time that a series

days concurrent injections 9 c.c. estrin (theelin) 450 R.U. Left ovary removed, 6.8 by 4.7 by 4.0, 92 mg. uterus 13.8 by 8.7. Progestin on day of operation and for 11 days (385 gm. total dose). No blood on lavage during treatment. Estrin (theelin) 2 c.c., 200 R.U., given on day following last progestin treatment. Continued 6 days (1,200 units total). Blood in vaginal lavage on third day estrin treatment. External blood on fourth day; on fifth day profuse bleeding with clots; on sixth day no external blood, few R.B.C. on lavage; on seventh day no R.B.C. Autopsy. Uterus 35.2 by 15.8 by 11.4. Bleeding during estrin treatment on fourth, fifth, sixth, and seventh days after last progestin treatment.

Monkey 138 ♀.—3,600 gm. Ten days A.P. 21 c.c. (7 gm. dried sheep gland) aqueous pyridine method. Concurrent estrin injection last 4 days (9 c.c., 450 R.U.). Ovariectomy eleventh day. Right ovary 139.3 mg. Left ovary 138.6 mg. Uterus 10.9 by 10.4. Progestin (1 c.c. = 35 gm.) 70 gm. daily for 11 days. Estrin started day following last progestin treatment. Vaginal lavages daily throughout. Animal tolerated progestin badly. Estrin 200 units daily for 11 days, on eleventh day bleeding. Autopsy on eleventh day. Uterus 33.0 by 14.8 by 12.0. Great loss of weight and effect of toxicity of extract. No pathologic lesions seen at autopsy.

Monkey 137 ♀.—3,700 gm. Right ovary removed, 6.6 by 4.1 by 4.8, 85 mg. Left ovary 7.0 by 3.5. A.P. subcutaneous 10 days (7 gm. dried sheep A.P. aqueous pyridine method). Last 3 days concurrent injection estrin (theelin) twice daily (total 500 units). Left ovary removed, 7.6 by 6.2 by 4.8, 133.3 mg. Progestin on day of operation and for 11 days 50 gm. daily, total 550 gm. fresh corpora lutea. Estrin (theelin) on day following last treatment 2 c.c. daily. Vaginal lavages daily. No R.B.C. on days 1, 2, 3, 4, 5, or 6. On day 7 good external flow, continuing through days 8, 9. Autopsy on ninth day after cessation of progestin. Uterus 35 by 14.8 by 9.0.

Monkey 166 ♀.—4,450 gm. Menstrual period October 2 to 5. Ovaries removed, right October 12 and left October 24. Uterus 11.7 by 9.1 mm., uterine bleeding following ovariectomy. Estrin 200 units daily (amniotin in oil) during bleeding (2 days) and for 5 days thereafter. Extract progestin (6 months old, 57 gm. fresh tissue daily, slightly more than 1 rabbit unit) for ten days. No R.B.C. in lavage in this period. Color faded by days 8 and 9. On day after last progestin treatment, estrin (amniotin in corn oil) 300 units daily. No R.B.C. in lavage on estrin days 1, 2, 3. On day 4, the fifth day after last progestin injection, external bleeding. Bleeding 3 days during continued estrin injections.

Progestin has prevented the usual and expected bleeding of estrin priveria and led to the formation of a typical progestational endometrium. When this endometrial condition has been established, as it is in the ovulatory cycle of the monkey or human being, subsequent menstruation, with its morphologic equivalents, occurred in the presence of large amounts of estrin.

#### DISCUSSION

The Allen-Corner hypothesis that menstruation is due to estrin priveria has been based largely on the experimental results on the monkey. The available data regarding the hormonal relations during the human cycle offer certain obstacles. The data in this respect are not so abundant as might be hoped but are quite uniform.



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Both Kaufmann (1932) and Clauberg (1933) have reported the production of progestational endometriums in ovariectomized women by the use of follicular hormone followed with corpus luteum hormone.

Loeser (1933), however, has observed the bleeding response in several cases. The patient in the first case, twenty-eight years of age, was one with primary amenorrhea. She was first treated with follicular hormone, 400,000 M.U. over a period of thirty-eight days, and this was followed by corpus luteum hormone, 40 Rab. U. for four days. Typical bleeding began two days after the last treatment and continued for five days.

The period of this treatment had been forty-four days. In the next experiment with the same patient it was reduced by one-half. Estrin, 330,000 M.U. for sixteen days and progestin, 50 rabbit units, for five days. Bleeding as before occurred one day after the last treatment, and lasted for six days. This was repeated with the same dosage and time factors and the bleeding was the same. The curetted specimens were studied by Robert Meyer and reported to be of the premenstrual stage which had not reached the end of the secretion phase.

In a second case, a thirty-eight-year-old primary amenorrheic, 300,000 M.U. of estrin and 50 rabbit units of progestin in twenty days resulted in bleeding on the second day after cessation of treatment of the progestin injections. Two other cases of secondary amenorrhea were similarly treated. The production of a pro gravid endometrium with good glycogen production is attested by Robert Meyer.

The present evidence of the human cycle thus leads us to believe that menstruation, usually in the human being from the degeneration of a pro gravid endometrium, occurs in the presence of an abundance of blood estrin. The experimental data also show that menstruation also occurs in the presence of a high estrin level and fortifies the opinion that when the corpus luteum ceases its secretion, the estrin present cannot further develop the endometrium or maintain its pro gravid phase. It then begins involution and menstruation takes place.

#### SUMMARY

1. It is generally accepted that in the mature monkey, uterine bleeding occurs after deprivation of the estrin supply of the animal by any method.

2. This bleeding can be prevented by the administration of a hormone of the corpus luteum, progestin. This prevention has been for the duration of the treatment, in one case as long as twenty-eight days, though usually for eleven or twelve days. Bleeding occurred three to five days after the cessation of progestin treatment, and only then.

3. Uterine bleeding which follows cessation of progestin therapy occurs within the expected time, even though estrin administration is instituted at once and continued until bleeding occurs.

4. Evidence from other investigators dealing with the human cycle is cited, indicating that in the human being also, in the ovulatory men-

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human fetus at birth was estimated to absorb from umbilical blood between 40 and 50 gm. of lipids per day, of which 75 per cent was phospholipids. These results suggested that the lipemia of pregnancy may be related to the uptake of lipids by the fetus in utero. It is recognized that this relation need not hold for every species of animals; in several species, for example cows, rats, and rabbits, there is actually a decrease in the blood lipids during pregnancy. Fat metabolism varies appreciably from one type of animal to another, especially between herbivora and carnivora, and the results obtained in one species should not be applied without reservation to the interpretation of the changes in another species.

The lipemia of pregnancy has at various times been proposed as a preparation for lactation, it being suggested that the increased concentration of blood lipids assists the production of milk fat by the mammary glands. This theory obviously applies more especially to the period following parturition and raises the question as to what happens to the lipemia of pregnancy once pregnancy is over. Although often suggested, it has never been satisfactorily proved that the blood lipids in the early puerperium are related to lactation. If there is a relation, then one should be able to demonstrate a difference in the blood lipids between women who lactate normally and those in whom the breasts are dried up for various reasons such as a still-born infant, etc. This method appeared quite feasible and was adopted in the present investigation to prove or disprove the point.

Apparently the only previous investigation of a similar nature was that of Herrmann and Neumann in 1912.<sup>4</sup> These authors used the semiquantitative methods then available to show that whole blood cholesterol and total lipid decreased during normal lactation but remained elevated when lactation did not occur. More recently, Harding and Downs<sup>5</sup> have shown that the "lipoid phosphorus" of blood plasma declines after delivery less rapidly if milk secretion is small. Practically all those who have reported on blood lipids during pregnancy (for list of references see Boyd<sup>2</sup>) have also included readings during the puerperium but did not contrast the changes in normal lactation with those in a "dry puerperium." In the present investigation all lipid groups present in whole blood, plasma and the red blood cells were separately estimated and compared in puerperae of these two types. The changes in the lipid composition of the white blood cells during the puerperium have been reported by Boyd.<sup>6</sup>

#### METHOD

The investigation was performed on twelve patients from the Obstetrical Divisions of the Strong Memorial Hospital. Seven of these were primiparas and five multiparas. In all of them pregnancy had been normal and delivery was not accompanied by any untoward event such as excessive bleeding, marked perineal tears, etc. In

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the fall being due principally to a decrease in neutral fat. Phospholipids exhibited very little change while the remaining blood lipids, namely free cholesterol and cholesterol esters, actually rose slightly in value. The changes in whole blood need not be described in any further detail since the results in plasma and the red blood cells were much more descriptive of what was taking place.

The lipid concentration of blood plasma was found to decline consistently after delivery in all cases where normal lactation occurred. On the other hand when the breasts were dried up, plasma lipids fell in value only while the breasts were filling, and then actually rose again as the breasts responded to treatment and began to shrink in volume. A typical example has been selected from each group of cases and presented in Figs. 1 and 2.

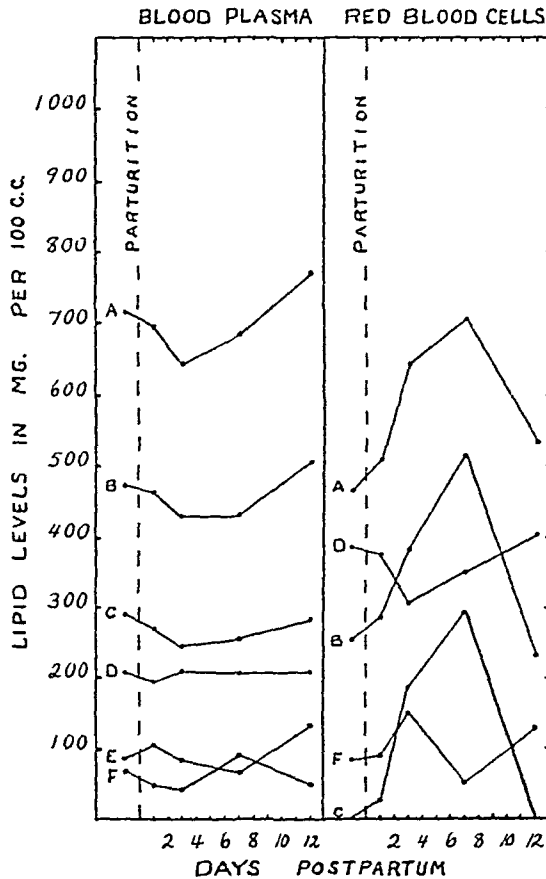


Fig. 2.—The concentration of lipids in blood plasma and the red blood cells during the puerperium in a forty-three-year-old para xi, child stillborn, breasts engorged on the third day postpartum but subsequently dried up. Curve A, total lipid; Curve B, total fatty acids; Curve C, neutral fat; Curve D, phospholipid; Curve E, ester cholesterol and all values equal to zero throughout; Curve F, free cholesterol!

The decline in value of plasma lipids during lactation was in a large part due to loss of plasma neutral fat. On the average, the concentration of plasma neutral fat fell from  $353 \pm 75$  mg. per cent at delivery to  $275 \pm 115$  mg. per cent at the twelfth day postpartum (the figures given are means  $\pm$  the standard deviation). After neutral fat, the greatest decrease was found in the phospholipids and next in the free cholesterol and ester cholesterol. Changes in the cholesterol fraction were comparatively slight.

When normal lactation was prevented by drying up the breasts, the downward trend in the concentration of puerperal plasma lipids was halted, as illustrated in Fig. 2. In the first three or four days of the puerperium, while the breasts were

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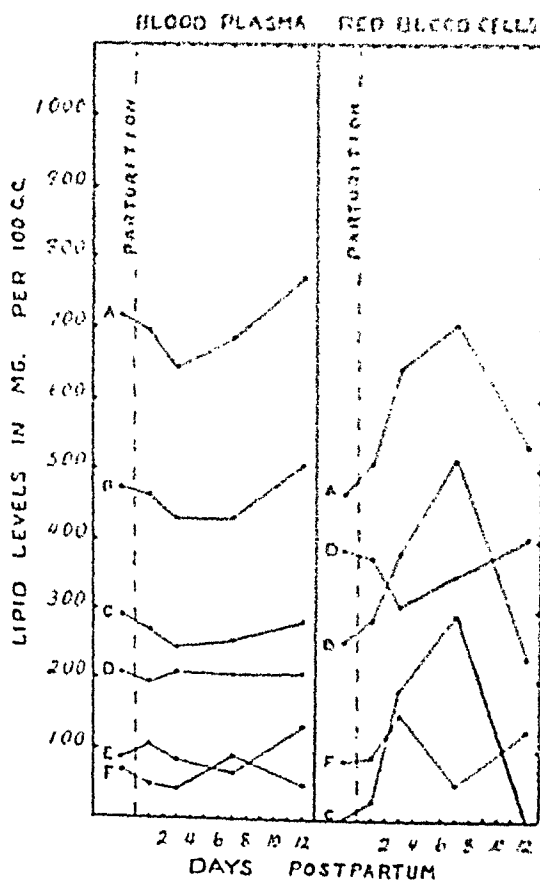


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TABLE I. THE IODINE NUMBERS OF TOTAL FATTY ACIDS AND PHOSPHOLIPID FATTY ACIDS IN BLOOD PLASMA DURING THE EARLY PUERPERIUM

CASE	MAMMARY GLANDS	IODINE NUMBER			
		BEFORE DELIVERY	1-3 DAYS POSTPARTUM	5-7 DAYS POSTPARTUM	10-12 DAYS POSTPARTUM
<i>Total Fatty Acids</i>					
1	Lactating	102	94	--	78
2	Lactating	122	81	80	--
3	Lactating	96	85	103	93
4	Lactating	88	68	81	80
5	Lactating	84	50	57	--
6	Lactating	82	63	76	84
7	Lactating	78	124	61	82
8	Lactating	78	81	86	--
9	Lactating	77	63	72	67
10	Dried up	98	81	78	86
11	Dried up	86	61	72	84
12	Dried up	66	61	71	72
Mean		88	76	76	81
<i>Phospholipid Fatty Acids</i>					
1	Lactating	174	102	--	88
2	Lactating	148	158	156	--
3	Lactating	142	103	112	135
4	Lactating	136	71	94	152
5	Lactating	121	69	92	116
6	Lactating	100	64	115	--
7	Lactating	96	127	130	--
8	Lactating	93	85	137	140
9	Lactating	78	62	65	117
10	Dried up	130	92	102	128
11	Dried up	105	73	96	128
12	Dried up	102	57	65	114
Mean		119	89	106	124

12 cases, reaching a mean value of 89. From then, in all except 2 cases, the iodine number of the phospholipid fatty acids rose steadily in value, reaching a mean of 106 at five to seven days postpartum and 124 or approximately normal<sup>1, 2</sup> at the tenth to twelfth days postpartum. These results indicate that the phospholipids of blood plasma after parturition exchange their fatty acids for fatty acids containing fewer double bonds; by the end of the second week of the puerperium the composition of plasma phospholipid has returned to normal, in terms of its iodine number.

#### DISCUSSION

The results of this investigation lead to certain further conclusions concerning fat metabolism during pregnancy. It has been shown that when milk is secreted by the breasts after delivery, the concentration of all lipids in blood plasma falls. The greatest decrease was found to occur in plasma neutral fat; next, in order, phospholipids; and finally the least change occurred in the cholesterol (free and ester) fraction. These changes, which resulted in the disappearance of the lipemia of



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of certain hormones or other effects, cannot be stated at present. The results indicate that the effect of drying up the breasts immediately after delivery is not confined to the breasts alone but is reflected by a change in body function generally.

Certain facts indicate that lactation may not be entirely responsible for the fall in plasma lipids after delivery. First, as noted before, the sequence by which lipids disappear from plasma after delivery is analogous to the sequence in the disappearance of other lipemias in which lactation obviously takes no part. Second, it has been shown that the composition of plasma fatty acids, as indicated by their iodine number, undergoes the same changes following parturition irrespective of the onset of normal lactation. And third, the lipid content of the red blood cells increases temporarily in the first week of the puerperium also independently of normal lactation. These changes are probably referable more particularly to the process by which the lipemia of pregnancy disappears rather than to the changes accompanying the onset of lactation. Since both of these factors come into play in the first week of the puerperium, one cannot state that lactation alone is the factor responsible for the decline in plasma lipid values. It is probably correct to conclude that lactation may *assist* in bringing the concentration of blood plasma lipids to normal values. But there is no doubt that the prevention of normal lactation results definitely in a lipemia.

In the lower animals, lactation may have an effect opposite to the above, i.e., it may cause a lipemia. Lactation produces a rise in blood lipids usually in those animals in which pregnancy causes a lipopenia or decrease in the value of blood lipids (for usage of the term "lipopenia," see Boyd<sup>9</sup>). Thus, lactation in the cow is accompanied by a rise in the value of all blood lipids,<sup>9, 10, 11, 12</sup> in rabbits the blood lipids rise in the puerperium independently of the occurrence of lactation,<sup>13</sup> while in dogs the values fall as in women.<sup>13</sup> It is difficult to reconcile these variations between species: there appear to be certain inherent differences in fat metabolism between species of animals, especially between herbivora and carnivora. The important conclusion relative to the present discussion is that experimental results obtained in animals should be applied by analogy to human subjects with the utmost caution.

Several explanations have been offered as to where the excessive amounts of blood lipids go to once pregnancy is over. It has been proposed that in the puerperium blood lipids are discharged through the bile,<sup>14</sup> in urine, sweat and feces,<sup>4</sup> and in milk. Most of these theories and the more recent discussion of them (see review by Boyd<sup>2</sup>) seem to imply that the fat content of blood is a static value. That is to say, these theories appear to take for granted that if a number of grams of lipids are removed from blood by the liver, kidneys, intestinal

of certain hormones or other effects, cannot be stated at present. The results indicate that the effect of drying up the breasts immediately after delivery is not confined to the breasts alone but is reflected by a change in body function generally.

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# THE EFFECT OF THEELIN ON THE HUMAN VAGINAL MUCOSA

ROBERT M. LEWIS, M.D., NEW HAVEN, CONN.

*(From the Department of Obstetrics and Gynecology, Yale University School of Medicine)*

AS EARLY as 1904 Joseph Halban<sup>1</sup> by brilliant reasoning arrived at the conclusion that certain phenomena observed in the generative system of the newborn human female depended upon a substance elaborated by the placenta and carried by the fetal-maternal circulation to the infant in utero. The truth of his belief has been surprisingly substantiated by recent discoveries in the field of the sex hormones and their functions.

Bayer and others had already shown that the uteri of newborn girls are larger than those of older children. This fact Bayer considered due to an atrophy following birth. Halban, with clearer insight attributed the enlargement of the uterus, breasts, and also probably that of the external genitalia of the newborn to the presence of a material derived from the placenta. Their diminution during the first weeks after birth he laid to their deprivation of this substance. The uterine blood vessels and mucosa of the newborn he notes in certain cases as presenting pictures "exquisitely like" the menstruating uteri of adults. Edgar Allen<sup>2</sup> and others have shown that in the immature female monkey an hypertrophy of the generative tract like that of the newborn can be reproduced by repeated subcutaneous injections of follicular hormone. Although Halban's autopsied specimens of ovaries, tubes, uteri, and external genitalia were carefully studied, the vaginas were in only a few instances noted as "injected."

It is of considerable interest, therefore, to find that the vaginal mucosa of the newborn girl shows on microscopic section what can best be interpreted as a reaction to the maternal hormones that is at least as striking as that of the uterus, breasts, or external genitalia, and also that during the first few weeks of life the histologic appearance of the vagina, which lacks the stimulus of the maternal hormone, changes enormously. This change apparently also occurs in the vaginas of children prematurely born. At least two instances which have come under our notice would suggest that such is the case.

At birth the vaginal mucosa of the premature or mature child shows a basal layer of compact cells with nuclei which take a deep stain in prepared microscopic sections. This cell layer is thrown into folds and varies in depth throughout its length. Superimposed upon it we find a remarkable series of layers of vacuolated cells which often contain nuclei. Mitotic figures are frequent in this layer. This zone consists of vacuolated cells 20 to 30 or more layers in depth. The surface may show fragmentation possibly a result of postmortem change. In

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conclusion that the same agent, namely theelin, must be responsible for the production of the tremendous number of superficial vacuolated cells in both instances.



Fig. 3.—Vaginal wall of child aged eight months after injections of theelin, 100 R.U. daily for ten days, total 1,000 R.U. Here the mucosa resembles that of the newborn child showing many layers of vacuolated, partly cornified or cornified squamous cells.



Fig. 4.—Vaginal mucosa of woman seven months pregnant. Specimen taken from a series studied with Dr. Herbert Thoms.

Hisaw<sup>4</sup> after reviewing the studies on the mucification of the vaginal mucosa of various rodents concludes, "these results very strongly indicate that theelin (in subthreshold doses) is either directly or indirectly responsible for vaginal mucification . . ." Probably the appearance of cells showing vacuolization in the human vagina is analogous to those showing mucification in the rat.

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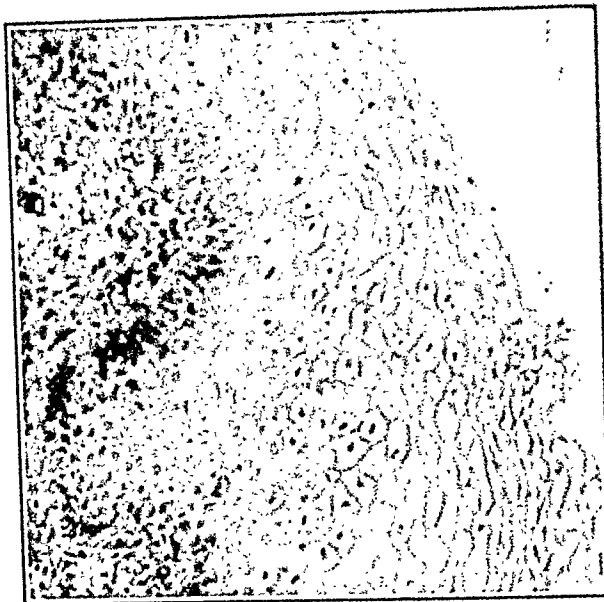


Fig. 3.—Vaginal wall of child aged eight months after injections of theelin, 150 R.U. daily for ten days, total 1,000 R.U. Here the mucosa resembles that of the newborn child showing many layers of vacuolated, partly cornified or cornified squamous cells.



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At the very end of pregnancy, soon after the high point of theelin in the maternal organism has passed, we would again expect marked vacuolization of the vaginal mucosa. Specimens of vaginal mucosa taken at the time of delivery show this condition to an extraordinary extent. Here we find (Fig. 5) a mucosa consisting of a basal zone of compact cells overlying a hyperemic submucosa with areas of extravasated blood and leucocytic infiltration. The deep zone of compact cells is usually from 4 to 6 layers in depth, these cells containing uniformly deep staining nuclei.

Overlying this is a series of remarkable layers of vacuolated cells, many of which contain nuclei in good condition, although some are pycnotic.

Superficially we find six to eight layers of more or less cornified flattened cells fragmented in some areas. The vacuolated cells and their arrangement again closely resemble those found in the vaginas of the newborn or in the specimens taken from children who have had a course of theelin injections. Again presumably the presence of theelin has been responsible for their production.

#### CONCLUSION

It seems evident that the presence of an excess of theelin (possibly also other hormones) in women produces vacuolization and multiplication of certain layers of cells in the vaginal mucosa. This vacuolization is strikingly evident in the newborn and in children injected with theelin. Biopsies of vaginal mucosa taken during pregnancy, when theelin is abundant, may show marked vacuolization on microscopic examination. In specimens taken at the time of delivery vacuolated cells in many layers are in evidence.

#### REFERENCES

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## SIGNS OF VITAMIN B DEFICIENCY

The symptoms of advanced deficiency disease need not be enlarged upon. Polyneuritis and pellagra are examples of prolonged vitamin B starvation. Both diseases are sufficiently well understood to make diagnosis fairly simple. The early signs of inadequacy—those which make their appearance before gross pathologic changes take place—are the signs with which we should be familiar. They may be mentioned in the order of their appearance, both in adults and in children, as follows:

1. Impairment of the digestive function—either mild or severe. One of the most severe manifestations is actual cessation of digestion.
2. Intestinal stasis; due to diminished neuromuscular control of the intestine.
3. Loss of appetite (often the first symptom for which relief is sought).
4. Constipation.
5. Restlessness.

Knowing that one or more of these symptoms are mentioned in over half of all new case histories it may be reasonable to assume, in the case of the pregnant woman, that vitamin B deficiency must be considered.

## WHAT AMOUNT OF VITAMIN B COMPLEX CONSTITUTES ADEQUACY?

In man, as well as in the experimental animal (rat), it has been shown<sup>18, 19</sup> that the best condition of health and nutrition requires that the food furnish much more of this vitamin complex than is needed to sustain normal growth. The actual number of B complex units necessary to sustain normal growth in an infant, in a five-, and in a ten-year-old child may vary inversally with the age-change. It has been shown, however, that for practical purposes we may expect 300 units to meet the growth requirements for an infant under one year. Optimum requirements are at least 25 per cent higher. From the sixth to the sixteenth year the optimum growth and maintenance requirements seem to be greatest; from 500 to 700 units being necessary. The unit of vitamin B complex, as used in this study, is that amount which when fed as a daily allowance to a standard rat results in net maintenance over an eight-week period.

To help determine the number of units which may be regarded as safe we have taken as a starting point, clinically, a study of the dietary of several hundred pregnant women. The vitamin B units are determined. Symptoms of deficiency disease are scrutinized and evaluated. The diet is supplemented with increasing amounts of vitamin concentrate or foods known to be rich in this vitamin. When symptoms of deficiency disappear the number of B complex units taken daily are estimated and this number is regarded as minimum for the individual. Hundreds of such tabulations have given the figures upon which some of our contentions are based.

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foods. Analysis of the dietary of several hundred women during these periods has shown that few, if any, of them get more than 12 to 15 per cent of their calories from protective foods. This study, then, also served as a test of our theory in this matter.

#### METHOD OF PROCEDURE

Two diet forms were prepared. The items were identical on both sheets. Those women who served as controls were advised to adhere to the articles of food named on the sheet. The actual amounts of food to be eaten were left entirely to their discretion. This seems to be the prevailing custom with many physicians, not excluding all of those who limit their work to obstetrics.

Those women who were to serve as test cases were given the same food list but, in addition, definite amounts of all food items were specified for them, and they were requested to live up to these specifications. The cereals advised were those known to be rich in minerals and in the B complex. In certain selected cases a mineral mixture containing iron, phosphorus, calcium, magnesium, sodium, and potassium was advised. This mixture was suggested to those women who, during previous pregnancies, were known to suffer serious demineralization.

TABLE II. FOOD CHART AS A GUIDE TO CONTROL AND TEST CASES

Cereals:	Mead's cereal,* cracked wheat, yellow corn meal, wheat bran, oats.
Fruits:	Apple, banana, cantaloupe, date, grape, grapefruit, lemon, orange, peach, pineapple, prune, strawberry. Also juice from these fruits.
Vegetables:	Asparagus, beans (all kinds), cabbage, carrot, celery, collard, cauliflower, lettuce, onion, parsnip, potato, tomato, spinach, turnip, cowpea, watercress, kale, beet and turnip greens, calavo.
Meat and Fish:	Haddock, whitefish, salmon, lean beef (steak, roast, ground chuck), brain, kidney, liver, bacon, lamb chop, squab and chicken.
Other Foods:	Egg, oyster (raw), milk, cheese, butter, cream, toasted bread, nuts, oil dressings. Tea, coffee, and beer were not denied.

#### *Suggestions for One Day (Control Cases)*

Breakfast:	Fruit juice, stewed fruit, egg, bacon, toast, cereal, milk or coffee.
Luncheon:	Lettuce or tomato (or combination) salad with oil dressing; portion of two green vegetables, fruit, milk, crackers or toast.
Dinner:	Serving of meat or fish; serving of at least two green vegetables; bread and butter, cheese or calavo or nuts, milk or coffee.

It has been observed by several collaborators that most pregnant women, with such a food list as a guide, will consume from 1,600 to 1,900 calories daily. By careful checking it is found that they obtain, as a rule, less than 15 per cent of their calories from the protective foods on the list. The study shows that the three meals are made up something after the following fashion:

Breakfast:	Small glass fruit juice (4 ounces); small dish cereal (1 to 2 small tablespoonfuls); one piece toast, one piece bacon; one cup coffee with cream and sugar.
Luncheon:	Meat or vegetable sandwich; baked apple, cup of tea or glass of milk (4 to 6 ounces).
Dinner:	Medium to small sized serving of meat or fish; one tablespoonful each of two cooked vegetables; one tablespoonful fruit or vegetable salad; one slice bread or toast; cup of tea or glass of milk (4 to 6 ounces).

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By referring to almost any table of food values it is discovered that such a breakfast supplies about 75 to 85 per cent of the calories from the nonprotective foods. About the same ratio holds true for luncheon and dinner.

The wisdom of such dietary imbalance must be challenged. Laboratory animals fed on a B complex deficient diet may be depended upon to perform in a definite manner. Litters are dropped prematurely. Only a few survive unless something is done. When sufficient amount of the B complex is fed to these weaklings, most of them immediately show signs of improvement. If the treated members of the litter survive and thrive and the untreated promptly die, it may be assumed that inadequacy of the B complex was, in some measure at least, the cause of the prematurity and the death of the young. Hundreds of litters of albino rats have been studied and the fate of the young not only observed but also predicted.

On the reverse side of the "Food Chart" handed to our test cases was outlined the amounts of various foods necessary to provide a certain number of B complex units (Table III).

TABLE III

	CALORIES	PROTECTIVE VIT. B	NON- PROTECTIVE
Breakfast:			
8 ounces fruit juice	100	76	--
4 ounces fruit pulp	45	48	--
1 egg	82	30	--
1 slice bacon	40	--	40
$\frac{1}{2}$ ounce butter	95	--	95
8 ounces milk	156	70	--
1 slice toast	15	--	15
	533	224	150
Luncheon:			
$\frac{1}{2}$ head lettuce	22	35	--
1 ounce oil dressing	182	--	182
3 ounces fresh vegetable	155	162	--
$\frac{1}{2}$ ounce butter	95	--	95
1 slice toast	15	--	15
4 ounces fresh fruit	40	48	--
8 ounces milk	156	70	--
	665	315	292
Dinner:			
4 ounces meat or fish	175	9	175
2 ounces creamed spinach	120	65	--
2 ounces other green veg.	112	125	--
$\frac{1}{2}$ ounce butter	95	--	95
1 slice rye crisp (3 x 3)	20	--	20
4 ripe olives (med.)	27	16	--
1 ounce cheese	45	--	45
$\frac{1}{2}$ ounce nuts or raisins	50	150	--
8 ounces milk	156	70	--
	800	426	335

It has been found that, with such a brief outline, many women can, over a period of weeks, vary their meals in a most satisfactory manner.

It will be observed that such a combination of foods supplied about 2,000 (1,998) calories daily, and that the B complex units amount to 965; not quite 50 per cent of the total calories. Brewer's yeast,\* two teaspoonfuls daily, supplies about

\*Refers to vitamin B and mineral preparations manufactured by Mead Johnson & Company.

400 units and this amount was advised for all patients who were disturbed by gas or constipation. In other words, our test cases all received considerably more than 50 per cent of their calories from protective foods; some of them as high as 75 or 80 per cent.

RESULTS

Time will not permit a detailed explanation of the results of the test. A summary of the findings show several interesting things (Table IV).

TABLE IV. CONTROL GROUP

Deliveries 116 (Primiparas 47; Multiparas 69)		
Low forceps 8, Section I; Version 1, normal 108		
Blood picture (first) Average: Hg 72%; R.B.C. 3,600,000; W.B.C. 8,200		
Taken day of delivery: Average: Hg 70%; R.B.C. 3,800,000; W.B.C. 8,750		
Incidence digestive impairment: Mild 36, moderate 5, severe 4 (38%)		
Loss of appetite: Before sixteenth week 5, thereafter 9 (12%)		
Intestinal stasis and constipation:		
Primiparas: Mild, 6, moderate 4, severe 16		(55%)
Multiparas: Mild 22, moderate 15, severe 12		(70%)
Headaches of vague origin (Blood pressure normal)		
Primiparas: 15		(30%)
Multiparas: 17		(24%)
Hemorrhage following delivery		
Low forceps 2		
Normal delivery 6		(6%)
(By hemorrhage was meant the loss of sufficient blood during or following delivery to produce clinical signs as pallor, changes in pulse, signs of shock, etc. Blood picture changes not taken into consideration.)		
<i>Lactating Ability</i>		
Adequate supply for 12 weeks	80	(69%)
Adequate supply for 16 weeks	59	(51%)
Adequate supply for 20 weeks	37	(32%)
Adequate supply for 24 weeks	17	(15%)
Adequate supply for 30 weeks	9	(8%)

The physical, mental, and emotional status of these women was considered. A rough estimate would declare about half of them in rather good general condition during pregnancy and during the lactation period. A number of them were victims of marked irritability and emotional instability during pregnancy. Most of these women were more unstable during their lactating period than during their pregnancy. As many as 10 per cent were regarded to be in fair to poor physical condition during the time they were under observation. Constipation and starvation stools were two outstanding problems with many of the group.

The physical, mental and emotional status of this group of women was considered and discussed. That, as a group, they were more satisfactory patients was the unanimous opinion. With but two or three exceptions they all reached their delivery dates in satisfactory condition. Many of the usual annoyances so often encountered during the lying-in period were conspicuous by their absence. Supervisors in the obstetric department of several of the hospitals reported good appetite, freedom from breast complications, and a much healthier and happier frame of

mind in these women than in the control group. In fairness it must be said that the state of mind of the test group was allowed to occupy a prominent place in their management. All of them, particularly the primiparas, were imbued with the idea that most of their fears were groundless; they were all encouraged to live considerably "outside of

TABLE V. TEST GROUP

Deliveries: 120 (Primiparas 60, Multiparas 60)		
Low forceps: 12, Section 3, Normal 105		
Blood picture (first) Average for group:		
Hg 75%; R.B.C. 3,750,000; W.B.C. 8,750		
Blood picture (just before delivery) Average:		
Hg 85%; R.B.C. 4,800,000; W.B.C. 11,200		
Incidence digestive impairment: Mild 18, moderate 6, severe 1		(20%)
Loss of appetite: Before sixteenth week 3, thereafter 4		(6%)
Intestinal stasis and constipation:		
Primiparas: Mild 4, moderate 7, severe: none		(18%)
Multiparas: Mild 15, moderate 8, severe: 1		(40%)
Headache of vague origin (Blood pressure normal)		
Primiparas: 4		(6½%)
Multiparas: 2		(3½%)
Hemorrhage following delivery: 2		(3½%)
(Loss of sufficient blood to produce clinical signs such as pallor, changes in pulse, signs of shock, etc.)		
<i>Lactating Ability</i>		
Adequate supply for 12 weeks	94	(78%)
Adequate supply for 16 weeks	91	(74%)
Adequate supply for 20 weeks	78	(65%)
Adequate supply for 24 weeks	45	(37%)
Adequate supply for 30 weeks	22	(18%)

themselves." We do not mean to say that the control group was slighted in this respect, but more interest was developed in the test group. A more satisfactory and interesting relationship existed between this group and their physicians.

#### IMPRESSIONS

We believe that vitamin B deficiency in the diet of pregnant and lactating women usually produces definite symptoms. Signs of demineralization are more pronounced in those women who obtain less than 50 per cent of their total calories from protective foods. The physical and mental health of man depends largely upon a normal blood picture and a normal ability to assimilate food. In this study it was observed that our test cases showed a much better blood picture than was true with the controls. While the matter of miscarriage has not been considered in this study, yet it is a matter of record that 5, or 4½ per cent, of the control group were threatened with this accident.

The test group escaped all such symptoms and, while this proves nothing, we may ultimately discover that dietary imbalance and poor assimilation may play a part in the etiology of some of these unexplainable accidents.



More calm and better milk producers were found in the test group. Severe signs of gastric and intestinal atony were almost entirely absent in the test group whereas in the control group these signs were met with in over 20 per cent of cases. We do not believe that this was purely coincidental. Previous views concerning some of the signs of vitamin B deficiency during pregnancy and lactation have been substantiated and strengthened. Vitamin B and mineral preparations used in this study were found to be satisfactory and reliable.

More infants should be breast fed; and for a longer period. The lactating ability of the mother rests very largely with the obstetrician rather than with the pediatrician. Most mothers cooperate satisfactorily if and when they are under adequate prenatal medical supervision. The surest method of weaning an infant is to insist that supplemental or complementary feedings be given so that the child will have regained its birth weight before leaving the hospital on the tenth to fourteenth day.

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During the years 1922 to 1931, inclusive, there were 8,346 mothers delivered at the Frauenklinik of the University of Innsbruck. Of these, 45 per cent were primigravidas and the rest were multigravidas. To these mothers were born 8,425 children more than 1,500 gm. in weight and 35 cm. in length. There were 38 maternal deaths and 335 fetal deaths, incidences of 0.45 and 3.99 per cent, respectively. There were 861 operations, excluding episiotomy, 10.3 per cent, distributed as follows:

OPERATION	NUMBER PERFORMED	PER CENT OF TOTAL NUMBER OF LABORS
Forceps	165	1.97
Version	113	1.35
Cesarean section	68	0.81
Manual dilatation of the cervix	51	0.61
Cervical incision and vaginal section	25	0.30
Embryotomy	30	0.36
There were 578 episiotomies performed, making a percentage of 6.94.		

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# A STUDY OF THE COLLAGEN OF THE PLACENTA

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THE purpose of this work has been to trace the development of collagen in the different parts of the placenta, the development of the basement membrane of the villi, and the relation of the above to nephritis, preeclamptic toxemia, and eclampsia. Also it has been interesting to observe the relation of the collagen formation to the development of chorionepithelioma. A series of placentas of varying ages have been fixed in Zenker's solution, and then stained by the Lee-Brown modification of Mallory's connective tissue stain. Also a few specimens of chorionepithelioma have been similarly treated.

In using the term "collagen" I am referring to a substance that stains dark blue with the connective tissue stain. Of course this stain is not specific. It also stains amyloid and other hyaline-like substances. However, I believe it to be true collagen as it is definitely not the result of an inflammatory process and also fibroglia can be demonstrated by the phosphotungstic acid stain on the cells that lie in the midst of this substance.

In early villi of two months' age, the loose stroma of the villi contains very few fine collagen fibers. There is no collagen in or around Langhans' layer and none in the syncytium. Large cell islands of trophoblasts that have not come in contact with maternal cells show a few very fine collagen threads. Wherever the trophoblasts come in contact with decidua, however, there is a fairly dense layer of collagen laid down (Fig. 1). It is also of interest to note that in the decidua itself there are only a few fine threads of collagen present. In the decidua vera there is practically no collagen. Therefore, it takes the contact of the fetal and maternal cells to stimulate the formation of collagen. A case of three months' pregnancy, where a hysterectomy was done because of a very large fibroid, shows a definite placenta accreta. There is practically no decidua present and the villi are firmly fastened to the uterine muscle. In this case there is a marked absence of collagen formation similar to that of the chorionepithelioma. It is a similar process except that the trophoblast cells have not acquired malignant characteristics.

In the specimens of tubal pregnancy (Fig. 2), except for occasional decidua-like cells in the tubal walls, there is no real decidual reaction

or defense against the invasion of the fetal cells. The result is large masses of trophoblasts containing very little collagen advancing through the muscle layers of the tubal wall to inevitable rupture if tubal abortion does not take place. There is here some defense reaction of the fibroblasts of the tubal wall in the formation of collagen, but it is not marked and entirely ineffective. Here as in placenta accreta the fetal cells show no malignant characteristics except their local invasive power. It does seem remarkable with the fetal cells spilled in the abdominal cavity and on the neighboring organs that there are no secondary growths. This again emphasizes the fact that the fetal cells do not grow outside of their own milieu unless they



Fig. 1.



Fig. 2.

Fig. 1.—Section showing invasion of trophoblast cells above. Note dense collagen around cells. In center is considerable destruction where maternal and fetal cells meet with blood clot and collagen. Below to right decidual cells.  $\times 400$ .

Fig. 2.—This section shows mass of fetal trophoblast invading tubal wall in tubal pregnancy. Note lack of collagen around trophoblast cells.  $\times 400$ .

have assumed malignant characteristics. The frequent finding of fetal cells in the lungs of normal pregnancies, carried there by the blood stream, and yet showing no signs of implantation or growth is proof of this point. Another point of interest in tubal pregnancy is the examination of the uterine decidua. The uterine decidua although well formed of typical decidual cells, is practically free of any collagen formation. There are a few fine collagen fibers present but without the presence of fetal cells the formation of collagen is practically absent.

The most extreme example of lack of collagen formation is found in studying various sections of chorionepithelioma, the invading cells of which consist of fetal trophoblasts that have assumed malignant characteristics (Fig. 3). These can be seen invading the entire uterine wall. In the first place there are large masses of fairly typical trophoblast cells invading the inner part of the uterine wall. There is a marked absence of collagen in these cell masses. In other words, although they have invaded the uterine wall, they appear similar to the early trophoblast of normal pregnancy that have not come in contact with maternal tissue. Around the edge of these invading masses is



Fig. 3.

Fig. 3.—A section of chorionepithelioma invading uterine wall. Note lack of collagen around invading cells as well as very thin layer of collagen around border.  $\times 400$ .



Fig. 4.

Fig. 4.—A normal full-term placenta showing characteristic basement membrane beneath syncytium.  $\times 1000$ .

a very thin line of collagen. Second, there are long thin columns of deeper invading trophoblast cells that are actually destroying such collagen as is present in normal uterine stroma. Third, the invasion of scattered trophoblastic cells throughout the entire uterine wall shows a markedly phagocytic action in regard to collagen as well as uterine muscle. The entire uterine wall shows the normal collagen of its connective tissue stroma or the remains of it, but no defense reaction of collagen formation. There is no definite contact layer between fetal and maternal cells and no maternal reaction to the fetal

invasion. This is the same as saying, there is no decidual reaction as there is no sign of any decidua present.

In the middle of pregnancy, four and a half to five months, there is a definite increase in the amount of collagen throughout the placenta. The stroma of the villi shows heavier collagen fibers. Around the early blood vessels there is a fairly thick layer of collagen already formed. Beneath the Langhans' layer that is disappearing rapidly there is a faint line of collagen between it and the stroma. This is the beginning basement membrane that will be taken up in more detail later. The syncytium itself shows no collagen formation. Most of the trophoblast cell islands have come in contact with maternal tissue and show considerable collagen in and about the cells. However, there are some islands still to be found without much collagen formation. The septa of the placenta at this stage already show a marked invasion by trophoblast and destruction of decidual cells. The stain used in this work shows a good differentiation between trophoblast and decidual cells. The trophoblast cells have a more granular cytoplasm, more irregular nuclei and stain a brighter yellow. The decidual cells have a homogeneous almost milky cytoplasm, clear cell outline and distinct round nuclei, and do not stain as brightly as the trophoblast cells. In the replacement of the decidual cells in the septa by trophoblast invasion, there is a dense collagen formation wherever the trophoblast cells have invaded, and this increases with the age of the placenta. The contact zone of maternal and fetal cells or the "Durchdringungzone" of Grosser<sup>2</sup> already shows a well-formed and fairly thick layer of collagen formation. The actual villi do not advance beyond this layer as a rule, although there are many trophoblast cells and many nucleated giant cells advancing beyond this into the compact layer of the decidua and even into the muscle. The compact layer of decidua at this period is still fairly broad and intact although the decidual cells have become somewhat flattened. There are some areas of collagen around the fetal cells that have invaded this decidua but as a whole it contains very little collagen.

At term the stroma of the villi is practically replaced by blood vessels which have a very thick surrounding layer of collagen. The Langhans' cells are largely absent and the syncytium contains no collagen. The syncytial buds both free and attached to villi show no collagen formation.

On the maternal side of Nitabuch's layer there are masses of cells surrounded individually by considerable collagen. There are large numbers of these cells in most placentas although there seem to be more in some than in others. They are quite large and stain bright yellow. They can be seen extending up the septa in large masses with

much collagen. Some are markedly degenerated and participate in small cystic formations. External to these cells is a thin layer of separated flattened cells with very little collagen. This thin layer of cells is in all stages of degeneration and is most likely composed of remaining decidual cells. As to the origin of the collagen or of the cells imbedded in it on the maternal side of the placenta, I do not feel that it can be definitely stated. The cells may be forming the collagen themselves, or it may have been formed by the degenerating decidual cells previous to their degeneration. I am inclined to think that these cells are fetal in origin for two reasons. In the first place the collagen surrounding them is not formed in decidua unless fetal cells are present. In the second place these cells show definite fibroglia with the phosphotungstic stain, while I have not been able to demonstrate fibroglia in true decidual cells.

In the study of the collagen of the placenta, it has been of special interest to trace the development of the basement membrane of the villous epithelium. This was described by Bonnet<sup>3</sup> in 1903. A definite basement membrane (Fig. 4) can be found in all ripe placentas, although it is hard to demonstrate in some villi, apparently due to the way they are cut. The beginning of the basement membrane can be clearly seen in some villi previous to the disappearance of Langhans' layer. When seen in these specimens, it lies between the villous stroma and Langhans' layer. Although the basement membrane becomes thicker and more distinct as the Langhans' layer disappears, its original position inside Langhans' layer would make it appear to have been formed by the fibroblasts of the villous stroma<sup>4</sup> rather than be a result of the degeneration of Langhans' cells. As the placenta grows older this basement membrane becomes more and more distinct until at term it is a very definite layer. This membrane has a definite thickness and staining reaction that is quite characteristic. Even in the old fibrotic type of placenta where the villi are small and with the Lee-Brown stain appear to be almost entirely filled with collagen, the basement membrane does not thicken in proportion. It is of interest when one considers the similarity of function between the villus of the placenta and the glomerulus of the kidney that each has a capillary bed surrounded by epithelium and a basement membrane.<sup>5</sup> Bell<sup>6</sup> has described as the typical lesion in the eclamptic kidney the thickening of the basement membrane of the capillaries of the glomerulus. With this in mind I studied the basement membrane in eclampsia, preeclamptic toxemia, and nephritis. In eclampsia I found a definite thickening of the basement membrane of the villi (Fig. 5). This appears in large groups of villi spread throughout the placenta mixed with other areas of villi where the thickening of the basement membrane is not definite. This thickening of the basement membrane

seems definitely to be due to an increased number of collagen fibers. It has a homogeneous appearance, but in certain areas separate and individual fibers can be made out. The thickening is not uniform as some parts of a given membrane are much thicker and denser than the rest. The irregular pointed projections of the membrane between the syncytial cells seem to be more marked. These projections appear more prominent and denser just beneath areas of marked proliferation of the syncytial cells. In certain severe preeclamptic toxemias similar although fewer groups of villi with thickened membranes are found (Fig. 6). In many milder toxemias no definite change in the membrane is found. In chronic nephritis no definite change in the membrane could be made out. Therefore, it would seem as if in



Fig. 5.



Fig. 6.

Fig. 5.—Villi from placenta of case of definite eclampsia at eight and one-half months' pregnancy. Note marked thickening of basement membrane. This placenta showed large areas of the above type of villi with some areas of normal appearing villi.  $\times 1000$ .

Fig. 6.—Villous from a case of severe preeclamptic toxemia in an eighteen-year-old girl. A cesarean section was done to avoid impending eclampsia. Placenta showed numerous areas of villi with thickened basement membrane as above.  $\times 1000$ .

eclampsia and severe preeclamptic toxemia, there is a definite thickening of the basement membrane of the villi which undoubtedly affects its permeability and powers of excretion and secretion.<sup>7</sup> This should not be confused with the thickening of the walls of the blood vessels in the physiologic endarteritis of the ripe placenta or the increase of the collagen of the stroma in old fibrous villi. It is the actual thickness of the basement membrane itself irrespective of the total amount of collagen in a given villus.

## SUMMARY

A study of placentas of varying ages has been made. The Lee-Brown modification of Mallory's connective tissue stain has been used. The purpose has been to trace the development of collagen. The formation of collagen has been shown to take place at the junction of the fetal and maternal cells. It is not formed in decidua where there are no fetal cells. There is a marked absence of collagen formation in placenta accreta, in tubal pregnancy, and in chorionepithelioma.

A definite basement membrane of the villous epithelium has been demonstrated in the latter half of pregnancy. This has a definite width and thickness according to the age of the placenta. In cases of eclampsia and severe preeclamptic toxemia, a definite thickening of the basement membrane has been demonstrated which is not found in the normal ripe placenta, in nephritis, or in mild toxemias.

## CONCLUSIONS

1. The formation of collagen around the fetal cells invading the decidua has been shown to take place in the normal development of the placenta. In certain abnormal conditions of the placenta this process breaks down.

2. The basement membrane of the villous epithelium can be clearly demonstrated by the Lee-Brown connective tissue stain in the latter half of pregnancy.

3. There appears to be a thickening of the basement membrane of the villi in eclampsia and in severe preeclamptic toxemia.

I wish to express my indebtedness to the Mallory Institute of Pathology for their assistance in this work.

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## UPPER URINARY TRACT INFECTIONS COMPLICATING PREGNANCY\*

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IN THIS paper we shall present some of the deductions which study of the female urinary tract in pregnancy, as well as the literature upon the subject, have allowed us to draw. We intend to deal with the normal changes in the urinary tract accompanying pregnancy, and shall attempt to show how these alterations predispose the woman to disease. In addition, we shall consider the pathologic processes that may ensue with some evaluation of their meaning to the woman, and shall hope to be able to indicate sound physiologic principles for combating them.

If we regard pregnancy in the woman simply as a biologic process, we find it in most respects admirably adapted to its purpose, but in others, either it is still in process of adaptation, or orthogenetic influences have brought about changes which are definitely deleterious to its purpose. By orthogenesis we mean that tendency in evolution which permits continued development in a given direction even though it be harmful to the species. Genealogic examples of this are the saber-toothed tiger whose maxillary equipment developed to such a remarkable degree that what was once a formidable armamentarium for attacking its prey became, finally, a hopeless impediment and was the most important factor in the extermination of the species. Other examples are the mammoth with its huge curving tusks, the Irish stag with its magnificent spread of antlers of over six feet, as well as many of the reptilia. From the studies of Grosser it seems very probable that certain of the developments of the human placenta, particularly the retardation of the rate of blood circulation, may be regarded as an example of the operation of this principle in the human species. It is possible that some of the toxemias as well, represent imperfections in adaptation of this biologic process to its environment. Whatever the true interpretation of these maladjustments or maladaptations may be, one comes to the conclusion that there are definite flaws in the process. One of these would seem to be our immediate concern in considering the cause of upper urinary tract disturbances in the pregnant woman.

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First let us consider some of the advantageous variations which take place in the organs concerned. Many of the tissues of the pelvis undergo hyperplastic changes characteristic of pregnancy. The endometrium lining the uterus more than doubles its depth producing the decidua, the cervical glands penetrate the myocervix converting it into a soft, succulent structure, the connective tissue of the broad ligament proliferates, forming a protective mechanism against infection, and the musculature of the uterus, vagina, ureters, and bladder hypertrophy in preparation for the duties they will eventually perform. In addition, there is increased vascularity and hyperemia of all the pelvic organs. These are but a few instances of the profound morphologic changes that take place. In addition, there are physiologic variations. The uterus is converted by chemical or hormonal influences from a small, hard, muscular viscus into a large flabby sac which is markedly insensitive to stimulation until term is approached. Similarly, the large bowel and the ureter are somewhat atonic and sluggish in action. Whether or not the same physiologic factors affect atonicity in all these smooth muscle structures is not known. However, their somewhat similar reaction to pregnancy is suggestive. It is known that some of the chemical substances or hormones present in the blood in large quantity during pregnancy have a relaxing effect upon the musculature of the uterus and bowel. The work of Knaus, and Reynolds, among others, has demonstrated satisfactorily that the corpus luteum hormone, progesterin, removes irritability from the smooth musculature of the uterus and makes it quite immune to many stimulating substances, such as pituitrin and adrenalin, which usually stimulate it to contraction. It is quite possible that the ureters and large bowel are somewhat similarly affected.

Other investigators, Westphal and Benda, have thought that this relaxation effect might be accounted for by the increased cholesterol circulating in the blood of the gravid woman. Still others, Stoeckel, Schumacher and Klasten, account for it in the general terms of "incretory intoxication."

Although the explanation may be somewhat in doubt, we have learned that the uterus, ureters, and large bowel undergo an atonic change, which commences during the early months of pregnancy and persists until the eighth month, when it slowly diminishes, so that at term the uterine musculature is not only irritable but contracts vigorously. We have observed much the same reaction in the ureter. As far as the uterus is concerned, this atony of the musculature is a beneficial physiologic phenomenon, being a safeguard against abortion, but in the ureter, as we shall see, it constitutes a hazard to the woman.

Since Cruveilhier and Sipple in 1843 described widely dilated ureters in the bodies of pregnant women upon whom they made postmortem

examinations, it has been suspected that there might be profound morphologic changes at work in these organs. However, not until the advent of the roentgenogram and safe contrast media, such as neoskiodan and sodium iodide, together with adequate technic for introducing them, has this suspicion become a certainty. We now know that moderate dilatation, elongation, and lateral displacement of the ureter, particularly upon the right side, are a normal concomitant of pregnancy in the woman in at least 80 per cent of the subjects studied, which now number in the thousands. In addition, there is frequently some dilatation of the renal pelvis and the left ureter. For many years attempts have been made to account for this phenomenon on the basis of the enlarged uterus with its contents, and the pressure they exert upon the pelvic brim. The fact that most of the widening of the ureter occurs above the linea terminalis and is seldom seen in the pelvic ureter is a strong point in support of this thesis. However, the fact that dilatation is frequently observed as early as the fourth month of pregnancy when the uterus is so small as not to be supposed to be capable of causing any considerable embarrassment, together with the observation that the dilatation is predominantly right-sided, has tended, at least partially, to discredit this explanation as being adequate. Some observers, Halban being among the first, have called attention to the common dextrorotation of the gravid uterus, pointing out that such torsion exerts tension upon left-sided structures and tends to kink and exert pressure upon those of the right side. Others (Kretschmer and Hofbauer) have shown the marked hyperplastic changes in the musculature and connective tissue of the vesical trigone and ureter, and have postulated a narrowed lumen with urinary back pressure as the cause of the widening of the superior portions of the tract.

It seems fairly clear that, with the exception of atony, none of these factors operating alone can definitely be assigned as the cause of the ureteral dilatation characteristic of pregnancy, because we have similar forces caused by large ovarian cysts and myomatous uteri acting in the nonpregnant woman, in whom this ureteral picture is seldom observed. We must, therefore, seek some cause which is a constant occurrence in pregnancy. This seems to be the loss of irritability of the smooth musculature of the ureter and kidney pelvis. Atonic muscles plus the weight and torsion of the uterus would seem to account for the findings completely. The ureter in its relaxed state is unable to expel the urine secreted by the kidney because of the steadily increasing weight upon it as it crosses the pelvic brim; therefore, it gradually dilates and in doing so contains an increasing column of more or less static urine. In the normal woman the amount of residual urine in the ureter and kidney pelvis varies from 10 to 60 c.c., and

occasionally in those who have had rapidly repeated pregnancies this may amount to much more, even 200 c.c. Following delivery the ureter quickly recovers its tone and involutes much as does the uterus. This process is complete usually in about two months' time, so that pyeloureterograms taken after this interval show a normal outline.

Residual urine, whether it occurs in the bladder, ureter or kidney pelvis, is a source of danger which has long been recognized by urologists, as it is prone to infection and once contaminated, allows of such rapid growth of microorganisms as to make cure difficult as long as the stagnation persists. The pregnant woman with her dilated ureters is, therefore, in constant hazard of developing an upper urinary tract infection.

If, then, we accept what seems to be an inescapable conclusion, that the normal pregnant woman develops what borders upon a pathologic dilatation of the upper urinary tract as a result of the fundamental anatomical and physiologic features of the gravid state, the question may justly be asked why this has come about. In answer we are forced to speculate, and there are some facts in comparative biology which may be of assistance. In the first place, woman is the only mammal which assumes the erect posture as the chief position during waking hours. Others affecting it such as the kangaroo and chimpanzee, do so only partially with frequent reversion to the horizontal. In doing so, when pregnant, they remove the weight of the gravid uterus from the pelvis and its contents. So far as we have been able to discover woman is the only mammal in which the ureters become dilated in pregnancy. We may perhaps be justified in concluding, therefore, as woman elected to become more and more upright in posture, the weight of the uterus, when pregnant, also came to be more constantly borne by the bony pelvis. As far as the ureters are concerned this may have been an event which natural forces have not completely succeeded in compensating, placing it in the category of a maladjustment of these organs to the evolutionary changes of the race.

The mechanism whereby infection of the renal pelvis takes place is a mooted question. Some observers, Kretschmer and others, feel that there is regurgitation of purulent urine from the bladder into the ureter, postulating a decompensation of the ureterovesical valves. Despite interesting work done to prove this theory, it does not seem particularly convincing as an explanation of the usual mechanism, for cystitis is not a common antecedent of ureteritis. Others have demonstrated the passage of bacteria from the bowel by way of the lymphatics to the region of the capsule of the right kidney (Franke), and others have pointed out the relationship of the incidence of pyelitis to the existence of foci of infection in teeth, tonsils, sinuses,

appendices, and gallbladder. Because the *Bacillus coli* is the invading organism in over 90 per cent of the individuals suffering with pyelitis, the lymphogenous route would seem to be by far the most likely. It is a well-established fact that the kidney excretes bacteria. Crabtree and Dodds find the *B. coli* contaminating the urine in from 11 to 14 per cent of the many gravid women whose ureteral urine they cultured, while in the puerperium the bladder urine was infected in as many as 70 per cent.

With these facts in mind, it is remarkable that we see pyelitis gravidarum in as few as 2 per cent of our patients, the usually accepted incidence. One is forced to the conclusion that there must be protective forces at work. This seems to have been demonstrated by Dresel, who studied the opsonic index in pregnancy with regard to *B. coli* and learned that this measure of immunity is increased tremendously in normal women and, moreover, that it is low in those individuals who develop pyelitis.

The onset of the disease is usually after the fifth month of pregnancy, and not infrequently in the puerperium when it is likely to be mistaken for uterine infection. It is somewhat more common in primigravidae than in others. There is usually a dull aching pain in the right flank associated with fever, chills, sweating, malaise, and sometimes nausea or vomiting. Occasionally this is preceded by dysuria and hematuria, but often not. Examination reveals a tender kidney, sometimes enlarged, with tenderness in the costovertebral angle and over the course of the ureter. The urine is cloudy and contains clumps of white blood cells and many bacteria. The latter are usually *B. coli* with sometimes a staphylococcus or streptococcus as a secondary invader. The temperature runs a hectic course with rises frequently accompanied by a chill. Blood culture done at this time seldom yields a growth of organisms, although they must be present at least in small numbers in the blood stream since the picture is that of bacteriemia. The disease is accompanied by a marked tendency to secondary anemia, presumably because of the hemolytic propensities of *B. coli*. With proper therapeutic measures the course of the disease is brief as far as the clinical symptoms are concerned, but unfortunately the disease lurks in the tract throughout pregnancy once it develops. This observation has given rise to the dictum that pyeloureteritis is never cured in pregnancy, a statement which is not absolutely true, but is a safe point of view for the clinician to assume. Ordinarily after a few days the temperature falls and the acute phase is past. However, not infrequently in those with more marked infection or more complete obstruction, as well as in neglected cases, the symptoms and fever may persist, in which case we are usually dealing with an invasion of the parenchyma of the kidney and the disease

has developed into pyelonephritis with a much more grave prognosis. The involvement of the renal secretory tissue by inflammatory processes, particularly if bilateral, carries with it the dangers of uremia as an immediate threat, and cortical damage due to fibrosis with impaired kidney function as an ultimate possibility.

The pathologic picture of pyeloureteritis is one of peripheral inflammation of the walls of the ureter and renal pelvis in the earliest stages, with hyperemia and edema as the outstanding features. As the process develops there is an exudate formed covering the involved areas which tends to flake off and float in the urine; this is the source of the clumped pus cells so characteristic in the catheterized specimen. In addition, there is tremendous infiltration of the tissues with phagocytic cells of blood and connective tissue origin. When the process is prolonged these latter become organized into permanent scar tissue and thus fibrose the structures involved, impairing blood supply and mobility. When the dilated ureter becomes extensively involved in this inflammatory process it never involutes completely after the termination of pregnancy, but forms what the German clinicians speak of as the "fixed ureter of pregnancy." Herein lies one of the great dangers of pyelitis in pregnancy. The woman may be left with a tract or tracts that harbor large amounts of residual urine and possess little or no peristaltic activity. Such a patient is extremely hard to rid of infection, even though many months of careful treatment be lavished upon her. In other words, we may have chronic ureteritis and pyelitis as sequelae. These patients are particularly prone to a renewal of the acute phase in subsequent pregnancies.

As a more serious pathologic process in the acute phase, we may have extension of the inflammation from the pelvis of the kidney into the peripelvic tissues surrounding the large renal blood sinuses, with the added dangers of blood stream infection. On the other hand, the process may attack the medullary and even the cortical portions of the kidney, in which event these areas are rendered inactive due to edema and infiltration of inflammatory cellular elements. The process may go further and produce localized, cortical abscesses and even sepsis and death. In the past two years we have had three such events in an experience of about eight thousand pregnant patients. It is not this possibility, however, that should most impress us; it is rather upon the milder and more chronic sequelae, which are much more frequent and have a profound and lasting effect on the lives of many women, that we should seek to place the greatest emphasis.

The treatment of pyelitis divides itself into two phases: the first concerns the acute phase, and the second the chronic. The febrile patient should have complete rest in bed, bland diet, a fluid intake of 5,000 c.c. per day, adequate saline catharsis, alkalies such as sodium

bicarbonate 2 gm. t.i.d., and frequent change of position. On this treatment a large proportion of patients will become afebrile in a few days with complete disappearance of symptoms. However, they should remain in bed a full week after the temperature has become normal. This improvement seldom means that the patient is cured, particularly if it is antepartum, as repeated urine examination will usually show a continuance of pus and bacteria. From this time onward, if there be no acute exacerbation, the patient should be considered as chronically infected, bearing in mind the constant danger of a return of the febrile phase both ante- and postpartum. She should continue the therapy outlined above in a modified form until term with great emphasis upon the horizontal side positions as frequently as is possible. During the postpartum period she should be followed at fortnightly intervals with urine examinations. If she continues to pass pus and bacteria, the affected urinary tract must be treated by moderate dilatation of the ureter and lavage of the kidney pelvis preferably with normal saline solution. We have tried a large number of mild antiseptics for this purpose and have come to the conclusion that the mechanical flushing with the improved drainage resulting from dilatation are the essential factors in obtaining a good result and that antiseptics have little to offer. We feel that the dilatation of the ureter in these chronic infections is most important as the inflammatory thickening and fibrosis of the ureter tends to narrow the lumen and thus impede drainage. Fortunately, most patients under this treatment respond in a relatively short time; others, about 30 per cent, have a much more prolonged course, stretching out in some instances for months. It should not be necessary to point out the importance of protecting a chronically inflamed urinary tract from the embarrassment of further pregnancies. A smoldering infection in an atonic ureter will flare up with remarkable regularity in a subsequent pregnancy.

When the intermittent fever continues, as it does in pyelonephritis despite rigorous treatment, one must view the situation as most grave. This is particularly true, if the infection is bilateral and if there is evidence of retention, such as diminished urinary output and elevation of the nonprotein or urea nitrogen content of the blood stream. Under these circumstances, the uterus should be evacuated by the simplest and quickest means. The improved drainage resulting from release of pressure upon the ureters, as well as the decrease in waste products emptied into the maternal blood stream, serve as a source of great relief and may be the deciding factors in the patient's course. Whereas the forcing of fluids is an important feature in the treatment of pyeloureteritis, it must be used with caution in the patient suffering with extensive pyelonephritis because the ability of the kidney

to excrete water is diminished. For this reason, pelvic lavage through the ureteral catheter or the use of an indwelling catheter is far more important in these patients than we have found it to be in those suffering from pyeloureteritis. Other features of the patient's care are expectant. The chief differences between the two groups of patients, pyeloureteritis on one hand, and pyelonephritis on the other, is that the treatment of the former is conservative in the acute phase, with persistent and prolonged follow-up in the chronic, whereas, in the latter our therapy must necessarily be radical in a fair percentage of patients if the woman is to be saved from being a permanent invalid. The difficulty lies in the clinical differentiation of one group from the other. They are not clear-cut entities, but merge into one another. However, a few points may serve as guides. One should always be apprehensive about bilateral lesions, so much so, that if the temperature and symptoms do not yield after five or six days of active therapy, frequent blood chemistry examinations should be made to detect the first appearance of an elevation in nonprotein nitrogen. If a definite elevation occurs and persists in the absence of vomiting, one should not hesitate to terminate the pregnancy. That this will impress many as radical there can be no doubt; however, as a result of prolonged trial of conservative methods, the trend is definitely toward the prompt termination of pregnancy in this type of case.

What is the prognosis in women who have had a sufficiently severe inflammatory infection of the upper urinary tract as to cause the fever and symptoms of pyeloureteritis or pyelonephritis? It has not been possible to answer this question until comparatively recently. Through the excellent work of Klaften, Crabtree, Dodds, Prather and Kretschmer, to name only a few, who have followed their patients carefully in the postpartum months, we now know that previously we were much too sanguine as to the eventual outcome from the point of view of both baby and mother. In brief, approximately 50 per cent of these patients, speaking of pyeloureteritis, will after three months be completely well, and furthermore they will in all probability not have a recurrence in a subsequent pregnancy. About 33 per cent will harbor the infection for a longer period of time and show some degree of permanent damage to the tract, such as persistent dilatation with hydroureter and hydronephrosis of slight or moderate degree. The remaining 10 to 15 per cent show very definite hydronephrosis and renal damage as evidenced by decreased ability to excrete urea or phenolsulphonephthalein. In addition, we have learned that a certain percentage of febrile patients in the puerperium who have been regarded as suffering from a uterine infection have, instead, a urinary infection. The fetal mortality is usually found to be approximately twice as high in the pregnancies as is experienced in normal pregnancy.



The more severe sequelae of pyeloureteritis and pyelonephritis form a challenge to the obstetrician. They occur in the neglected patients in whom the condition has not been recognized or in whom proper treatment has not been carried out. We must learn how to diagnose and properly care for these important and far too frequent complications and sequelae of pregnancy. We recognize the importance of, and place a very proper emphasis upon the toxemias, but the urinary tract has been neglected. It is to be hoped that the future will show a very marked increase in appreciation of the significance of these lesions on the part of American obstetricians.

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### THE PELVIC FASCIA\*

#### A. HISTOLOGIC STRUCTURE OF THE PLANES OF TISSUE USED IN THE "FASCIA OVERLAPPING" OPERATION

#### B. AN ATTEMPT TO CORRELATE CONFLICTING VIEWS

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**B**EFORE describing the pelvic fascia it is important to consider that within the abdominal and pelvic cavities there are two quite different systems of fascia. The one, a strong dense plane of true fascia lining the muscular and bony walls of the abdomen and pelvis, is designated as muscle fascia (Tandler),<sup>1</sup> deep intraabdominal fascia (Gallaudet),<sup>2</sup> or voluntary fascia (Davies).<sup>3</sup> From the abdomen it extends downward into the pelvis and at the origin of the levator ani muscle from the lateral pelvic wall it splits into three layers. One extends caudally to line the lateral wall of the ischiorectal space, the second covers the inferior surface of the levator and the third, the superior levator or supraanal fascia, covers the cranial surface of the levator and coccygeus muscles. The inferior and superior levator fascias meet at the genital hiatus and fuse around the free border of the levator muscle.

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The other, the subperitoneal connective tissue, so named by Tandler and called by Gallaudet the superficial intraabdominal fascia and by Daves the involuntary fascia, in the early development of the body is a loose areolar structure, which, as the organs of the pelvis are formed and move into their final positions, is developed into planes and bands which, from time to time have been given special names. This rather loosely woven connective tissue structure with its various condensed bands and planes fills the space between the peritoneum and the deep or muscle fascia lining the two great cavities. In some areas it is only a thin areolar substance, while in others it fills rather large spaces with compact bands of fibrous tissue, extending from the pelvic wall to the viscera.

One of these condensations is the Mackenrodt or cardinal ligament. This structure, considered by Mackenrodt to be an important support to the uterus, is described by Tandler as a condensation of the subperitoneal connective tissue about the uterine vessels as they approach the uterus. In my own dissections this structure was noted and found to be as described by Tandler. Koster<sup>4</sup> in histologic study confirms this opinion. He and Tandler state that because of its structure the cardinal ligament can be of no supportive or surgical importance. Davies although agreeing to its structure believes that it helps to support the uterus. To the writer, although it seems likely that even such loosely woven strands of connective tissue must play some part in the natural support of the pelvic organs, there is considerable doubt as to their surgical importance. The intimate relation between the fibrous bundles of this structure and the uterine vessels and the ureter would make suturing a dangerous procedure.

Another important plane of pelvic fascia about which there is some difference of opinion is the fascia endopelvina. This is a broad, thin, fibrous sheet arising from the pelvic floor lateral to the vagina and extending from the lower border of the pubis toward the anterior aspect of the sacrum. This layer is designated as the visceral layer of the pelvic fascia by Cunningham,<sup>5</sup> and is stated by him to spring "from the parietal layer immediately above the origin of the levator ani and that, as it runs toward the medial plane it encloses the pelvic viscera." Tandler states that this broad sheet of connective tissue which he says is the lowest plane of the subperitoneal connective tissue and to which he applied the name *tela endopelvina*, since he limits the term fascia to true muscle fascia, extends from the symphysis in a laterally convex curve to the ischial spine, from which it radiates toward the connective tissue on the anterior aspect of the sacrum. He further states that "the whole expansive structure is, accordingly, laterally convex and medially cut three times concave around the bladder, vagina, and rectum."

In a recent article I<sup>6</sup> described this structure and stated that a broad sheet of fascia was found to arise from the fascia covering the superior surface of the levator ani muscle. Its line of origin extended from the lateral portion of the inferior border of the body of the pubis back to a point just medial to the spine of the ischium. Its dorsal border blends by means of loose areolar tissue with the fascia covering the pelvic aspect of the sacrum. To this layer I gave the name "main sheet" of pelvic fascia. This main sheet in the dorsal half of the pelvis rises cranially 5 to 6 cm. to form the uterosacral ligaments. Ventrally, at the lateral border of the cervix and vagina it divides to surround these organs forming the prevaginal and retrovaginal layers of fascia. This description was found to agree in general with that of Tandler's tela endopelvina. I could not agree, however, with Tandler and others that this layer has its origin in the subperitoneal connective tissue. On further study it was noted that the superior levator fascia covering the cranial surface of that muscle did not do so in a complete and uninterrupted manner. At a point about 1 or 2 cm. from the origin of the muscle, it was found that the superior levator fascia left the muscle to form the fascia endopelvina (main sheet of pelvic fascia), and it was demonstrated that the latter was, therefore, composed of two layers. Therefore, the fascia endopelvina is defined as a double layer of fascia extending as a mesentery-like structure from the pelvic floor to the lateral margin of the vagina over the walls of which its two leaves spread.

In an histologic study made by me<sup>7</sup> it was found, in a section of the pelvic organs of a twenty-two-month-old infant, that the thin fascia endopelvina passed behind the rectum and gave no evidence of its origin from the superior levator fascia (Fig. 7, Ref. 7). This presents evidence more to substantiate Tandler, Davies and others, than my own gross dissections described above. However, Halban has stated that the fascia endopelvina is a direct continuation of the fascia endoabdominalis, that it lines the pelvic cavity and *covers the uterus, vagina, and bladder*. This point is, however, more academic than clinical.

The next point for debate is the presence and origin of a definite perivaginal fascia. I have stated that the "main sheet," fascia endopelvina, splits to surround the vagina, the lateral layer forming a definite prevaginal fascia and the medial leaf a retrovaginal fascia. This agrees with Tandler, Cunningham and many others who describe a definite dissectable layer of fascia around the vagina.

Goff<sup>8</sup> was one of the first to dispute this generally accepted point of view, and it is largely to him we owe our knowledge of the importance of histologic study of the pelvic connective tissue. Goff states in his conclusions that "there is a thin layer of fascia of areolar type between the anterior vaginal wall and the bladder, and a similar layer of areolar fascia between the posterior vaginal wall and the rectum. These layers, he continues, unite at the side of the vagina to form the perivaginal fascia

which is a part of the fascia endopelvina. However, he states that the areolar character of this fascia makes it impossible to dissect it as an individual layer." Koster agrees with Goff in this. Goff, Koster and the writer agree that no plane of fascia exists between the urethra and vagina.

In my second paper I reported an histologic study of the perivaginal connective tissue of an adult nullipara and two infants. The sections were taken through a plane between the cervix and the upper end of the urethra and after the usual celloidin technic of embedding, were stained with hematoxylin, eosin and orange G. for connective tissue differentiation. At the lateral margin, anteriorly, loose but definite connective tissue strands were found on, and fused with, the muscle of the vaginal wall. Toward the center they became very thin until they could scarcely be distinguished. In some areas definite fibroelastic bundles were seen. The blood vessels approaching the vaginal wall were surrounded by loose areolar tissue which fused with the thin layer of fascia endopelvina as it reached the lateral vaginal wall. Along the posterior wall a more definite and continuous strand extended across the vagina closely fused with the vaginal musculature and traced laterally as a layer of the fascia endopelvina.

From this study I was able to modify and to some extent clarify my former opinions. Although these perivaginal layers, continuous with the endopelvic fascia, were present as definite bands of connective tissue of varying density and were present as early as the eighth month of life; they were in the main too thin to be easily dissectable.

It is evident from the foregoing study and from the work of Goff and of Koster that definite dissectible planes of fascia do not surround the vagina. Therefore, it becomes important to determine the structure of the broad planes of tissue obtained in the dissecting room and at the operating table. Bissel<sup>9</sup> removed sections of the anterior vaginal wall during operations for cystocele and found in them no evidence of fascia. In this regard, Koster makes the following statement: "In our operative material we have never been able to demonstrate any fascia in the rectovaginal or vesicovaginal septa. The only tissue to be found there, other than the mucosa is a loose, areolar connective tissue which can have no restraining or supportive value."

In the study to be reported here, tissue was removed from the anterior and posterior fascial planes of the vagina at operation. In obtaining specimens of the prevaginal "fascia" the typical Rawls<sup>10</sup>-Neel<sup>11</sup> "fascia overlapping" operation was done. A strip was taken from the outer third of the so-called fascia. This part was chosen because my former studies had shown the fascia to be denser at this point. This tissue was mounted on gauze and labelled so as to determine the vaginal and vesical aspects, embedded with the usual celloidin technic, cut and stained the hematoxylin, eosin and orange G. for connective tissue dif-

ferentiation. To obtain the sections of retrovaginal "fascia," this layer was exposed by carefully dissecting away the vaginal mucosa according to the method of Clark.<sup>12</sup> A firm thin layer of glistening tissue was, as usual, exposed. Sections were taken from this, carefully labelled and



Fig. 1.—Section of tissue removed from the anterior vaginal wall during fascia overlapping operation. Most of the lower half is composed of muscle bands with strands of fascia between them. There is a broad band of fascia extending obliquely upward across the upper half of section. Note wavy lines of elastic tissue, left center. Vesicle aspect is uppermost.



Fig. 2.—Section of dissected layer from posterior vaginal wall. In this section is seen very little muscle. Most of tissue is a compact connective tissue, with here and there strands of muscle. The rectal aspect is below.

treated with same technic as described above. With the stain used, the muscle appears a light red and the connective and fibroelastic tissues are stained a pale yellow.

The specimen (Fig. 1) removed from the anterior wall is found to be made up of the many bands of muscle, blood vessels of varying size, areolar tissue and fibro-

elastic connective tissue. These bundles appear between the muscle fibers throughout the entire section, but over the vesical aspect of this tissue at its most lateral point, there is a marked condensation of connective tissue containing many strands of fibroelastic tissue.

The specimen (Fig. 2) removed from the posterior vaginal wall, although containing some muscle fibers is made up principally of a rather compact connective tissue with strands of fibroelastic tissue interspersed. Over the rectal aspect of the tissue the density of the connective tissue is increased. In general the fascial structure of these specimens agrees with that described in my former paper.

It is apparent from this study that although definite broad firm sheets of tissue can be dissected from the vaginal walls, they are not composed of fascia alone, but of muscle, connective tissue and compact strands of fibroelastic tissue, the latter intermingling with muscle bundles but appearing as definite broad strands along the surface of the vaginal musculature. The muscle is more in evidence in sections obtained from the anterior wall. In a previous report I demonstrated that these strands of connective tissue are continuous with the fascia endopelvina, a fact also noted by Tandler and others.

For the past ten years I have used these musculofascial planes as the principal supportive factor in the surgical treatment of uterine prolapse. The results have been quite satisfactory and will be reported in a later paper.

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Ellenberg, S. L.: The Sedimentation Reaction in the Newborn, J. Lab. & Clin. Med. 19: 944, 1934.

Ellenberg investigated the sedimentation rate in newborn infants by the Linzenmeir macromethod. The blood was drawn from the anterior fontanel. The ages varied from two to ten days. The sedimentation time in the normal newborn infant ranged from seven to twenty-three hours, with the average sedimentation speed for the entire neonatal period at fifteen hours as compared with two hours which is considered normal in adults. There is also a tendency for the sedimentation reaction to become less prolonged as the infant grows older.

W. B. SERBIN.

## CHORIONEPITHELIOMA WITH A LONG LATENT PERIOD\*

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THIS case of chorionepithelioma is reported chiefly to emphasize the fact that a long insidious, latent period may intervene between the original pregnancy and the subsequent malignant tumor. Fortunately, we now possess hormone tests by means of which the diagnosis may be established in suspected cases during this dormant period, long before secondary metastatic manifestations make the condition obvious.

The simple invasion of the myometrium by trophoblastic, syncytial wandering cells, or multiform giant cells, may occur in any case of normal pregnancy. Likewise, there may occur prolonged retention of placental remnants as reported by Tritsch, who mentions cases in which placental tissue remained in utero for varying periods of from one week to six years without symptoms. Ries reported a case in which he found degenerated villi in the veins and walls of a uterus removed for fibroid eighteen years after the last pregnancy. If, weeks or months after a delivery, miscarriage, or hydatid mole, large masses of cells of fetal origin, which appear to be actively proliferating and replacing areas of the myometrium, are found, we have a potential malignancy.

A point, however, about which there appears to be but very indefinite knowledge, is how long such fetal elements may remain dormant and yet potentially active in the maternal organism after the termination of the gestation proper. In other words, how long after the last pregnancy may a tumor conceivably arise from such cells. Marchand, whose pioneer studies of chorionepithelioma date back to 1895, stated, even at that time, that we have no definite data for determining how long chorionic epithelium may remain alive in a closed vessel lumen, or a healed-over placental rest. The average interval in most of the cases reported has varied from one to twelve months. When the interim has been longer, there arises the suspicion that there has been an intervening pregnancy with early miscarriage which has been overlooked. A sufficient number of cases have been reported in which the interposing dormant period between the last demonstrable pregnancy and the development of a definite chorionepithelioma, either in the uterus or elsewhere, has been of very considerable length. This tends to establish with certainty the fact that far-reaching changes in the maternal organisms are capable of converting into malignant cells fetal elements which were encased within it in a friendly, inactive state for years, or decades, thus giving rise to a malignant tumor of the type under discussion. As

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indisputable evidence are those cases of chorionepithelioma appearing after the menopause. The most comprehensive article on the subject is by Krosing (1909) with a complete résumé of 21 cases reported up to that time, to which she added one of her own. We have collected 25 additional cases which have appeared since in the literature. Of these 46 cases, the latent period has varied from one to thirty years. A further analysis of this material reveals the following:

- 10 cases appeared in the third decade
- 11 cases appeared in the fourth decade
- 10 cases appeared in the fifth decade
- 13 cases appeared in the sixth decade

Of particular importance is the fact that 23 cases appeared after the menopause.

- 15 cases followed hydatid mole
- 14 cases followed normal full-term delivery
- 14 cases followed miscarriage

#### CASE REPORT

Patient, M. G., twenty-eight years of age, suffered the usual childhood diseases which left no residual pathology. At twelve years of age, following the death of a friend, she developed a marked fear of death. This was so pronounced that she experienced a nervous collapse several times prior to her marriage at twenty-one years of age, and about once a year after marriage. It was her custom never to be unescorted on a trip, or even a shopping tour, lest she become ill among strangers. In spite of this unusual mental complex, she was a very highly regarded teacher at school.

During December of 1930, at the age of twenty-five, two and one-half years prior to the time she was seen by us, the patient became pregnant for the first time. When she was four and one-half months gravid she spontaneously miscarried. An attending gynecologist at a local hospital performed a curettage for retained secundines. As she continued to bleed, a second curettage was performed ten days later. Examination of the curettings revealed no evidence of chorionepithelioma. Vaginal bleeding persisted and a third curettage was performed about two weeks after the second. One of the pathologists at the hospital thought these curettings were suspicious of chorionepithelioma. However, careful examination of the slides by a number of prominent pathologists throughout the city failed to reveal any evidence of malignancy. The last curettings were obtained more than three weeks after the miscarriage. Bleeding ceased soon after the third curettage, and the patient was discharged as cured.

For a period of two years thereafter she enjoyed unusually good health. She indulged in competitive sports with no evidence of fatigue. The first sign of illness made its appearance during May, 1933, about two and one-half years after her pregnancy. There had been no evidence of a subsequent conception during the interim. A scant menstrual period occurred in May, followed by some intermenstrual staining. During this period it was noted that the patient was becoming progressively paler. She began to suffer from weakness and headaches. Repeated pelvic examinations showed a small uterus of normal consistency. A complete general examination failed to reveal any cause for her anemia. Glandular and hemitonic medications were given with no effect. At the end of May the hemoglobin was 45 per cent



and the erythrocyte count 2,000,000 per c.mm. A thorough hematologic study failed to reveal any evidence of a blood dyscrasia. The anemia continued to be rapidly progressive and the patient began to vomit. This was attributed to the liver extract given by mouth, which had always caused nausea. Repeated chest examinations were negative. At this time we recalled the patient's history of a miscarriage two and one half years previously, followed by continued bleeding and repeated curettages. Mindful of the possibility of a chorionepithelioma following a long latent period, a Friedman test was done and proved to be strongly positive. Hospitalization was urged for more intensive investigation, but was refused. Because of her marked weakness and severe anemia, a blood transfusion was given at home, about the middle of June. On the following day a profuse hemorrhage occurred from a small bluish mass which had appeared on the perineum, above the anal sphincter. This growth, which was cystic and about the size of a marble, had the appearance of a thrombosed hemorrhoid.

The patient was admitted to the Israel Zion Hospital. The perineal mass, which had already become necrotic and ulcerated, was excised. It proved to be a chorion-



Fig. 1.—Anal wall showing submucosal syncytial cell portion of chorionepithelioma.

epithelioma. An x-ray of the chest on the following day showed the lungs to be studded with metastases. Both lung fields contained many rounded deposits, ranging in size from one to three inches in diameter. Two days after the metastatic deposits were demonstrated, the patient began to cough, and from this time on she exhibited increasing evidence of the malignancy of her condition. Painful cough with bloody expectoration, while mild at first, became very discomforting and most difficult to control. Vomiting became usual after each meal, as did also severe abdominal pain. At no time was there more than slight vaginal bleeding, or any palpable pelvic pathology. Severe frontal headaches were common and weakness was marked. The abdomen was distended and tender and the liver enlarged to as low as four fingers below the costal margin. With all these distressing symptoms her mental faculties remained acute until she passed into a coma six hours before death.

The laboratory report of the excised anal nodule is as follows:

The submucosal connective tissue, right beneath the epidermis, was the seat of a tumor mass which was necrotic to a certain extent. Islands of tumor tissue consisted of polygonal cells, similar to the Langhans' cells of the chorion. These cells were quite polymorphous and their nuclei showed considerable variations as to size

and shape. Mitoses were frequent. There were also scattered syncytial protoplasmal masses which contained a large number of nuclei, some vascular and some hyperchromatic.

The clinical value of the Aschheim-Zondek test in doubtful cases during the dormant period, cannot be too strongly emphasized. Previous to the utilization of this test, the diagnosis of chorionepithelioma was not made until we had a palpable uterine mass, positive curettings, or pulmonary or vaginal metastases. Curettage has been notoriously unsatisfactory owing to the possible location of the tumor at a distance from the endometrium. The suggestion of Vineberg to perform a vaginal hysterotomy and digitally explore the interior of the uterus has



Fig. 2.



Fig. 3.

Fig. 2.—Metastatic chorionepithelioma in rectum. Note central sheets of syncytial cells surrounded by masses of Langhans' cells.

Fig. 3.—High power of inset of Fig. 2. The two cell-types of chorionepithelioma clearly shown here.

been a considerable advance. The microscopic examination of the curettings is further complicated by the fact that the chorionic epithelium is normally a proliferative and invasive tissue showing a tendency to persist and penetrate to a considerable depth into the uterine musculature. This is especially marked when the syncytial coverings proliferate for no accountable reason and form polypoid processes which invade the surrounding tissue and lodge in the uterine and even in distant veins (Schmorl).

In 1929 Fels and Rossler demonstrated that hydatid mole and chorionepithelioma excrete many times more of hormone than the normally

pregnant, and that *quantitative* estimation by the fractional method of hormone excreted is an accurate guide in differentiating hydatid mole from uterine bleeding in the course of pregnancy due to other causes. Further investigations revealed that the presence of increasing quantities of hormone two weeks after the termination of normal pregnancy, or eight weeks after a molar pregnancy, is pathognomonic of chorionepithelioma. Thus far, approximately 50 cases of chorionepithelioma have been studied by means of the Aschheim-Zondek test, proving the value of the test in the diagnosis and prognosis of hydatid mole and chorionepithelioma. Estimation of quantitative differences in evaluating a persistent Aschheim-Zondek reaction is most important, and though clinical manifestations may be absent, an amount of gonadotropic substance in the urine in excess of 20,000 mouse units per liter, indicates an early chorionepithelioma. Levinthal and Saphir report a case of early chorionepithelioma diagnosed and operated upon solely on the basis of the laboratory findings of a strongly positive Aschheim-Zondek test with quantitatively 333,000 mouse units per liter of urine, in a patient who had expelled a hydatid mole four and one-half months previously.

#### SUMMARY AND CONCLUSIONS

A case is reported of the occurrence in a woman aged twenty-eight years, of a vaginal tumor possessing the histologic structure of a malignant chorionepithelioma two and one-half years after the last demonstrable pregnancy.

In view of the number of well-authenticated similar cases reported in the literature, we are forced to the conclusion that, whereas in the vast majority of cases all fetal elements are destroyed by the maternal tissue within a comparatively short time after the termination of pregnancy, in exceptional instances fetal epithelia may remain dormant in the maternal host, either at the placental site or elsewhere, for months or years, then to be, by some unknown agency, stimulated to malignant proliferation. The fact that many of these cases have developed long after the menopause would effectually disprove the theory that in all such cases an intervening pregnancy has escaped detection. It is to be regretted that the Aschheim-Zondek test was not utilized earlier in the course of this case, in which event a prompt hysterectomy might have stayed the progress of the disease.

## REPORT OF A CASE OF LUTEOMA WITH REVIEW OF THE LITERATURE

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GLYNN<sup>1</sup> used the term "luteoma" to describe lutein cell tumors. He reviewed the literature up to 1920, and collected fourteen ovarian tumors described as "lutein in origin"; of these nine were fully recorded, five briefly recorded. In this same article Glynn has collected ten cases reported as "ovarian hypernephromas," and in his discussion he presents evidence that these "ovarian hypernephromas" are probably of lutein cell origin.

Novak and TeLinde<sup>2</sup> did not consider the evidence for the lutein origin of all the fourteen cases mentioned above convincing, and objected to all five of the briefly recorded cases and specifically to two of the remaining nine. One of these reported by Schaller and Pforringer, in 1899, as an instance of carcinomatous degeneration following cystic transformation of the corpora, Novak and TeLinde point out is merely an example of multiple theca lutein cysts of the ovary associated with hydatid mole. In this case such a mole was expelled from the uterus twelve days after operation. The other case, reported by Grouzdew in 1903, was objected to because after operation the tumor recurred in the lymphatic glands and on the peritoneum as a spindle cell sarcoma.

In a review of the literature since 1920 we were able to find three cases reported as luteomas, those of Wolfe,<sup>3</sup> Cosaccesco,<sup>4</sup> and McIntyre.<sup>5</sup>

The following is reported as an additional case:

E. F., aged twenty-six, a colored married woman admitted to the Charity Hospital April 16, 1934. Her chief complaints were pains in the left lower abdomen for six weeks, and an amenorrhea of nine months' duration. She had two children, ages five and ten, normal labors and puerperiums. No abortions or miscarriages. Nothing of importance in the family, urinary, or gastrointestinal histories. Her menses began at thirteen, interval and duration perfectly normal until 1930, when she had irregular frequent bleeding. After three months of such irregular bleeding she states that she had a "vaginal operation," following which she had no further irregularities until 1933. The exact nature of this operation is unknown, as the patient was operated upon in another hospital and the record could not be obtained. She was told at that time that she had a "small cyst on one ovary."

During March, April, May, and June of 1933 she had vaginal bleeding nearly every day, using three or four pads. Associated was a cramplike discomfort in the lower abdomen, never severe. In July, 1933, without treatment, the bleeding checked and there followed a period of amenorrhea, until her admission in April, 1934. During the six weeks preceding admission she had pulling, dragging sensations with an occasional cramplike pain in the lower left abdomen.

*Examination.*—Temperature 99°, pulse 82, respirations 20, blood pressure 152/84. Urine negative. Red blood cells 4,000,000 c.mm. Hemoglobin 85 per cent (Talqvist), Wassermann negative, sedimentation time three hours. General development good; slight hypertension. Secretion could be expressed from both breasts. Abdominal examination revealed no masses or tenderness. The pelvic examination revealed

moderate relaxation of the perineum and small lacerations of the cervix. The fundus was found to be normal in size and position and freely movable. The right adnexa were normal to palpation. In the left adnexal region there was an irregular, hard mass, about the size of a large lemon, freely movable and not tender.

*Operation.*—April 24, 1934, laparotomy. A yellowish solid tumor of the left ovary, about 7 by 4 by 3 cm. in size, was found. The tunica and serous coat seemed to be everywhere intact. No adhesions were noted about the tumor. The right ovary was small, of normal consistency, and a small developing follicle presented at the surface. Both tubes and the fundus of the uterus were normal. The parametrium and the culdesac were normal to inspection and palpation. A left salpingo-oophorectomy and an appendectomy were done.

The postoperative course was uneventful. The incision healed by primary union. The patient was discharged May 3, 1934. The discharge examination revealed secretion still present in both breasts. There was no induration or tenderness in either adnexa, the uterus was in good position and freely movable.

*Follow-up.*—The patient was seen again on June 18, 1934. She stated that on May 20, twenty-six days after operation, she had a normal menstrual period of four days. No dysmenorrhea. Examination at this time revealed secretion in the



Fig. 1.—Longitudinal section of ovary.

right breast, but none in the left. The pelvic examination revealed the uterus freely movable; no tenderness or masses in the adnexa. The patient has been seen each month until Nov. 8, 1934. She has been in good health and has menstruated every twenty-six or twenty-seven days, duration three to four days. No dysmenorrhea.

*Pathologic Examination.*—The tube showed no pathologic changes of note. The ovary measured 7 by 4 by 3 cm. Several small cysts were seen, filled with a clear yellow fluid. On section (Fig. 1), there was seen near the surface of the ovary, and extending toward the hilum, a yellow growth, of firm consistency which made up the larger part of the ovary. No cysts were seen in the yellow areas, and the capsule of the ovary seemed to be everywhere intact.

Histologically the germinal epithelial layer was not well defined, the cells appearing normal. The tunica was well defined and not invaded by tumor cells. The bulk of the organ was made up of epithelial alveoli supported by a cellular fibrous stroma. The shape and the size of the alveoli varied, and in some areas small clusters of cells were found suggesting rosette arrangement. Surrounding the tumor mass was seen a thin shell of ovarian stroma, compressed, which showed primordial follicles, an occasional old follicle cyst and several old corpora albicantes. A striking feature was that in the examination of a number of sections of the ovary only one very early developing follicle was noted; follicle development seemed to be arrested.

The component epithelial cell showed slight variation in structure. The majority of the cells were large, round, ovoid, or polygonal in form, the cell outline being distinct. The cytoplasm was abundant, finely granular in appearance, but staining freely with eosin, and in many places a vacuolated appearance was presented. The nuclei were deep staining, mostly eccentrically placed (Fig. 2).

Less frequently smaller round or ovoid cells were seen with a deeper staining granular cytoplasm, their nuclei being vesicular and more centrally placed. This type of cell was especially noted in the small clusters or nests of cells (Fig. 3).

In some of the smaller alveoli (Fig. 4), the cells showed a mosaic arrangement. These cells were pale, some presenting a vacuolated appearance, the nuclei flattened out against the cell membrane; some were crescentic, suggesting a cell heavily laden with fat. The cell outlines were very distinct. Infrequently here one finds cells with a centrally placed nucleus.



Fig. 2.



Fig. 3.

Fig. 2.—High power of an area showing the structure of the component epithelial cell.

Fig. 3.—Low power of an area showing small clusters of cells.

In some areas (Fig. 5), the resemblance to a normal corpus luteum was striking, a core of cellular fibrous tissue being seen surrounded by luteinlike cells with fibrous tissue trabecula going to and from this core, dividing the cells into irregular alveoli. In these areas small vessels were seen, and the fibrous tissue trabecula seemed in places to be continuous with the adventitia of the vessels.

Intermingled with the tumor elements regressing corpora lutea were seen, and clusters of tumor cells seemed to be encroaching upon them. No mitotic figures were found. Degeneration was infrequent. The fibrous tissue stroma was of the spindle cell type and was mature. Its distribution was irregular; in some places, as in diffuse parts of the growth, only fine septa were found, in others it was found as compact zones about the alveoli.

Dr. Emil Novak was kind enough to examine a section of this tumor, and in a personal communication added a very interesting comment, which in part is as fol-

lows: "The feature which interested me most was that in some areas the constituent cells looked much more like granulosa cells than like lutein cells, and that the tendency of the cells in these regions to group themselves in small clusters and rosettes seemed quite typical of the more common granulosa cell tumor. In other areas, on the other hand, the large polyhedral, vacuolated appearance of the cells



Fig. 4.—Section showing small alveoli.

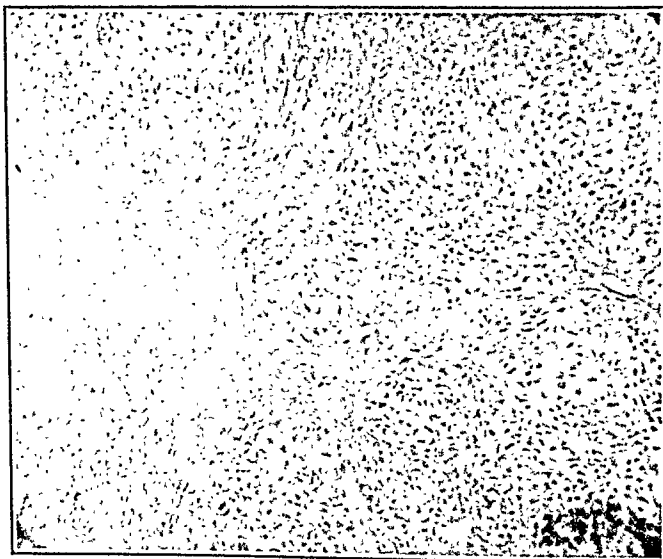


Fig. 5.—Section showing a core of cellular fibrous tissue surrounded by luteinlike cells.

and their tendency to alveolar arrangement made their resemblance to lutein cells very striking. . . . The granulosa cell appearance in parts of the section . . . lends support to the view held by many of us that the so-called luteoma is probably a granulosa-cell tumor in which the constituent cells have undergone more or less conversion into lutein cells, and that it does not arise, for example, from the transient lutein cells of the corpora lutea in the adult ovary." This possible rela-

tion of luteomas and granulosa-cell tumors is brought out in the recent study of granulosa-cell tumors by Novak and Brawner.<sup>7</sup> At the suggestion of Dr. Novak, special fat stains were made which showed the cells to be rich in lipoids.

### SUMMARY

Since Glynn's review of the literature in 1920, we have been able to collect three cases reported as lutein cell tumors, to which we add one case.

In the case reported by S. A. Wolfe it is interesting to note that the tumor was bilateral, and that menstrual disturbances were present only two months before operation, and were of the metrorrhagic type. The left ovary was not enlarged, and though no report of its consistency was noted at operation, pathologically it was described as being of normal consistency. No note of mitotic figures was made, and the tumor was well encapsulated.

In the case reported by A. Cosacresco et al., the removal of an ovarian tumor of lutein origin was followed by normal menstruation after an amenorrhea of eight years, and during the first two and one-half years following removal of this tumor, there was a marked regression of masculine characteristics acquired during the six years preceding operation. It must be recalled that an ovarian graft was done at operation, but the authors noted that they too believed that this played no part in the clinical improvement. The symptomatology certainly suggested the possibility of an arrhenoblastoma (Meyers<sup>8</sup>), but there is nothing in the pathologic findings reported to suggest this.

In the case reported briefly by McIntyre as a "malignant luteinoma," both the author and Bell and Datnow expressed doubt as to the origin of the tumor.

In our case the amenorrhea of nine months, followed by normal menstruation twenty-six days after the removal of a lutein cell tumor, is very interesting, and is clinical evidence of the hormonal activity of the tumor cells. In this respect the clinical picture is similar to the case of Cosacresco et al., where after an amenorrhea of eight years, normal periods followed the removal of a lutein cell tumor. Unfortunately the tumor was fixed by formaldehyde before the exact nature of the tumor was known and a study of the hormone content of it could not be made.

The metrorrhagia of four months preceding the amenorrhea in our case is interesting also. If luteomas are luteinized granulosa-cell tumors, it serves as an explanation of this combination of symptoms.

It is unfortunate that in the cases collected since 1920 a curettage of the uterus was not done, as a study of the endometrial pattern with a lutein cell tumor should prove interesting.

In the review of cases since 1920, with the exception of the case reported by McIntyre in which the diagnosis is questionable, we find no pathologic evidence of malignancy.

We wish to express our thanks to Dr. Emil Novak for his helpful suggestions and to Dr. C. G. Collins for his excellent photographs.

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## ANEMIA OF PREGNANCY

### A STUDY OF 60 CASES OF THE HYPOCHROMATIC TYPE

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**A**N EXAMINATION of the literature on anemia of pregnancy reveals a divergence and confusion of opinion regarding classification, cause, and treatment. This confusion results in part from a different approach to the subject by various authors. Most of the research on this subject has been done with laboratory animals, but our final opinion must be based on the response of the human subject to the various factors involved.

Although any type of anemia may be associated with pregnancy, there are two types resulting from the pregnancy itself, the pernicious and a true secondary anemia of the chlorotic or hypochromatic type. I will discuss only the latter group.

Due to the fact that pregnant women develop a varying degree of hydremia, some authorities have attempted to explain the blood changes of pregnancy on the basis of an increased blood volume, believing it to be physiologic. The results obtained by other investigators suggest that this anemia is due to the unusual demand for iron by the growing fetus and that this iron demand causes a depletion in the iron reserve of the mother.

For the past year I have made a study of the hypochromatic anemia of pregnancy. I have selected for this study sixty private patients. All patients having infections, hemorrhage, nephritis, or any apparent cause for anemia were excluded. These patients were given an adequate and balanced diet consisting of an ample supply of protein, both cooked and raw leafy vegetables, milk, and raw and cooked fruits. The red cell counts and hemoglobin determinations were taken at various times during the pregnancy and on the first day following delivery. The Sahli method was used for the estimation of hemoglobin.

I divided the patients into three groups. The first group consisted of untreated patients. The second group was given copper and iron therapy for a period of two months, following which they were given reduced iron for two months, and subsequently liver extract for two months. The third group was given copper and iron therapy throughout the prenatal period.

Chart 1 shows the red counts of forty-three untreated patients during the first trimester and the first day postpartum. It will be seen that these levels are practically the same (67 per cent). Had determinations been made on these patients a short time before delivery, they would have been lower as a result of reduction in blood volume following delivery.

Chart 2 gives the composite study of the results obtained from three different types of treatment. The group on copper and iron therapy showed an increase in their hemoglobin after two months of treatment. This group was then given reduced iron for a period of two months with the resultant decrease in the hemoglobin and red counts. They were then given liver extract with a subsequent improvement in their blood picture. The blood did not return to the levels previously obtained from the administration of copper and iron.

Chart 3 shows the average hemoglobin and red cell counts of a group of patients taking copper and iron throughout pregnancy. There is a gradual improvement in both hemoglobin levels and red cell counts before delivery and a slight drop in the

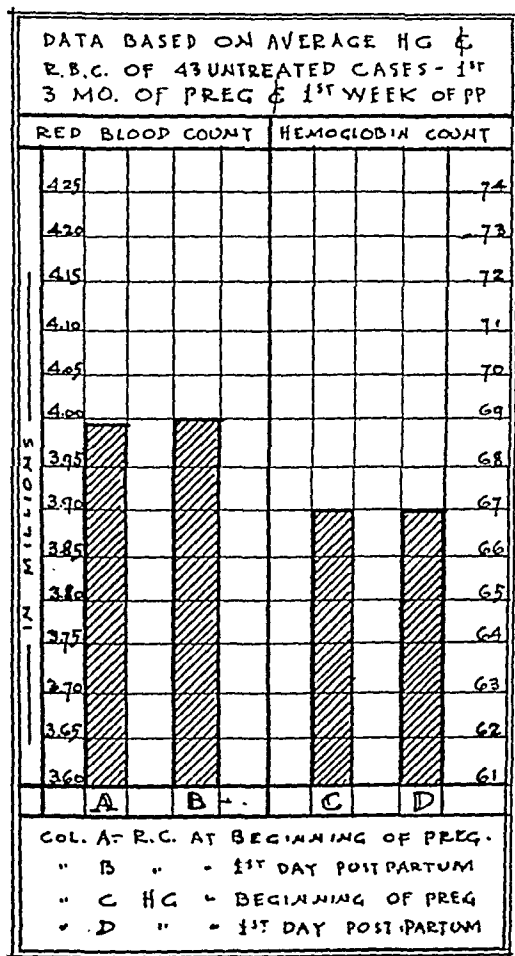


Chart 1.

red count following delivery, although the hemoglobin is at a higher level. These results are contrary to those obtained by Adamson<sup>1</sup> on untreated patients. My results tend to show that this anemia is not physiologic, for if this were true we would expect no improvement from treatment.

The patients studied in my series showed a hypochromatic or chlorotic type of anemia. The hemoglobin is reduced to a greater degree than the blood cells, and therefore, there is a low color index.

Clinical observations show that large amounts of liver can be effective in regeneration of blood following chronic blood loss. It should be reserved for use in the treatment of pernicious anemia, in which it

is most effective. In secondary anemia it is usually less potent and is less easy to take than copper and iron salts. Liver extract caused an improvement in the secondary anemia of pregnancy, but this improvement was less than that obtained by the copper and iron therapy (Chart 2). Steenbock<sup>2</sup> removed the copper and iron from liver extract by electrolysis and found the residue quite inactive. He believes that the value of liver in secondary anemia is due to the copper and iron present. Minot says of liver extract, "These extracts are not used with significant effect in secondary anemia and many patients have

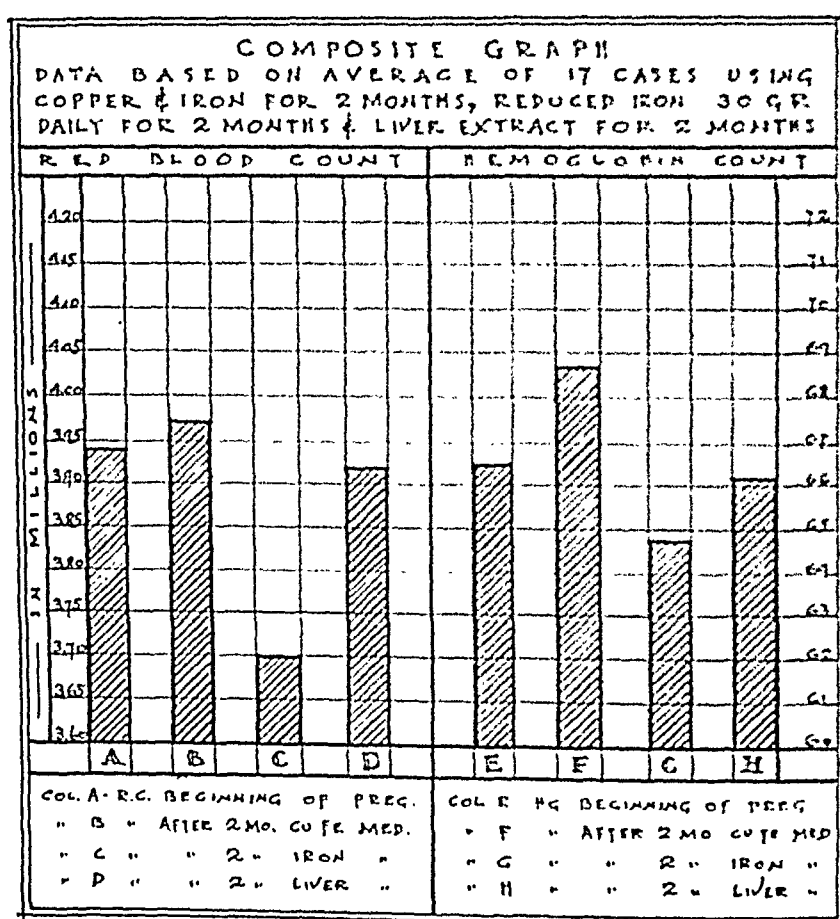


Chart 2.

wasted money and effort in buying and taking such products which cannot be expected to benefit them."

The pernicious anemia of pregnancy, in my series (macrocytic pernicious anemia of pregnancy) was not encountered. This group is characterized by Castle,<sup>3</sup> Whitby,<sup>4</sup> Mussey,<sup>5</sup> et al. by a high color index, megalocytosis with or without signs of blood regeneration, and is similar to Addison's pernicious anemia. These cases were first reported by Channing in 1842. According to Whitby<sup>3</sup> this condition is rare, especially in temperate climates. This type of pernicious anemia is controversial. Some claim it has a tendency to recur with

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each pregnancy with more severity, while others believe it continues between pregnancies and is likely to become a true pernicious anemia. Abortion may be indicated in this type of anemia.

Even with an anemia in the mother, the infants are born with a normal amount of hemoglobin and a normal red cell count which rapidly diminishes during the first few weeks of life. This is probably due to the insufficient supply of iron in the milk diet. The baby derives a supply of copper and iron from the mother even when the mother's copper and iron supply is inadequate for her own needs. If

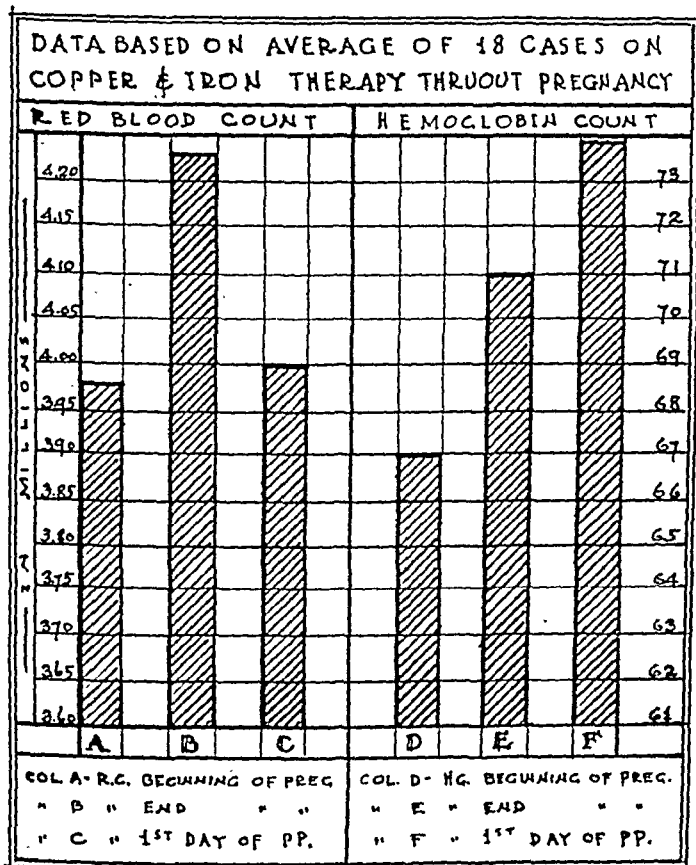


Chart 3.

sufficient copper and iron is not furnished to the mother during pregnancy, there may be an inadequate storage of these metals in the baby's tissues, resulting in the development of a secondary anemia during the first few weeks of the baby's life. Since the building materials used in the formation of the fetal blood are derived from the maternal organism, a condition analagous to chronic blood loss is present.

The Medical Research Council of England published a comprehensive investigation conducted by Dr. Helen Mackay<sup>6</sup> in East London from 1925 to 1930, on nutritional anemias of infancy, and their possible association with the iron supply of the mother, and its influence on

the amount stored in the fetal liver. They expressed this opinion, "It is probable that anemia in the mother predisposes to anemia in the child."

In watching the erythrocyte count and the hemoglobin levels of various patients, both with and without treatment, I have occasionally observed sudden and marked variations which were not dependent on any evident change in physical well-being. I have thought that these changes were due to sudden alterations in blood volume, and I believe that the evaluation of a therapeutic procedure in anemia of pregnancy must be gained by the study of a group of patients rather than the individual. It would seem that hydremia is a factor to be considered. I am confident that it is not the only factor operating, as my results show. This view is shared by Galloway<sup>7</sup> (1927), who says, "So far there has been little scientific or chemical evidence to substantiate the theory that secondary anemia is due entirely to hydremia."

The analysis and dosage of medication used in this study appears in Table I.

TABLE 1. MEDICATION CHART

PREPARATION	FE.	CU.	DOSAGE
Reduced iron	95%	0.01%	0.65 gm. t.i.d.
Copper and iron (Copperin A.)	32 mg.	0.1 mg.	3 capsules per day
Liver extract (Lilly or Merrill)	0.011%	0.003%	Represents 200 to 400 gm. fresh liver daily, depend- ing upon tolerance

This study suggests the following conclusions:

1. Secondary anemia of pregnancy is not physiologic but is caused by a constant drain on the copper and iron reserve of the mother by the demand of the growing fetus. It should be called a nutritional anemia of pregnancy, and is somewhat analagous to the nutritional anemia of infancy.

2. Patients taking copper and iron showed a gradual improvement in both red cell count and hemoglobin levels.

3. Patients taking reduced iron showed a gradual reduction in both red cells and hemoglobin.

4. Diet alone does not seem to furnish a sufficient amount of these basic metallic elements.

5. Macrocytic (pernicious) anemia of pregnancy did not occur in this group and is rare in this locality.

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# DIATHERMY IN THE TREATMENT OF PELVIC PATHOLOGY\*

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SINCE it is so well established that heat is useful in the treatment of pelvic pathology, it is not the purpose of this paper to reiterate an admitted fact. It is my desire to discuss the use of electrically created heat in different pelvic conditions that present themselves in a large clinic. The application of ordinary forms of heat to the pelvis is through douches, Sitz baths, hot water bottles, electric pads. With diathermy, however, the electrodes that touch the patient are not themselves warm, so that no conductive heat is given to the patient; the electrical energy applied is converted directly into heat. This is the essential feature which makes diathermy supreme as a method of creating heat in the pelvis, thereby inducing a physiologic hyperemia. Of course, other methods will produce a mild rise in temperature in the tissues, but electricity can produce as much temperature as desired, and the effects last for a much longer time after this treatment than with other methods.

The whole question of apparatus has never been universally decided, and it, therefore, seems fitting to express a few conclusions drawn from a very extensive clinical experience. I know many of the commercial salesmen will disagree with some of these statements, but they are only interested in selling machines and electrodes manufactured by their companies and have not the same attitude of mind as doctors whose primary interest is in obtaining satisfactory results in the treatment of their patients.

Small diathermy machines cannot produce results comparable to those obtained with large, high voltage machines. In electrical treatments of pelvic conditions, the object is to create heat in the tissues. This is done by the conversion of quantities or amperes of electrical energy. An ampere is a unit of volume of current. In order to get this electrical current evenly and smoothly distributed throughout a mass of tissue, it is necessary to have sufficient pressure to overcome varying resistances and supply ample amperage to every part. Voltage means pressure, and therefore to do efficient work, there must be sufficient voltage as well as amperage. This fact is borne out by clinical experience, and it is impractical to attempt pelvic treatments with a small machine.

\*Read before the Section of Obstetrics and Gynecology, New York Academy of Medicine, December 18, 1934.

The new method of electrically creating heat in tissues by the use of so-called radio wave machines with electrodes *not* applied to the body as diathermy electrodes is now well known. With this method the entire effect is one of high voltage with just sufficient amperage. This kind of treatment has a great future in gynecology after its limitations have been sufficiently studied. The method by which these radio wave machines function is also a factor in the effects produced in treatments with ordinary diathermy machines. The advantage of the latter is that heat is produced both ways, whereas the radio waves generate the heat by a single process. In both methods, however, high voltage is a very great essential, and satisfactory results can only be obtained by large, powerful machines.

As for the electrodes containing thermometers, when one has had experience with a certain machine and these thermometer-containing electrodes, it is possible to draw approximate conclusions as to the amount of heat generated in the tissues by the thermometer reading. Diathermy electrodes are not heated by the diathermy current. They are constructed of metals that are good conductors of electricity, and the heat is only generated in the nonconducting tissues. The effect of the current on the electrodes themselves is nil, and any heating of them is due to the secondary heating of the metal by the surrounding tissues. The amount of heat generated in the tissues immediately in contact with the electrodes varies with the voltage of the machine used, and therefore, the same electrode will give different readings with different machines on the same patient. Therefore, one should not be guided by these thermometers. Experience alone teaches what dosage should be administered.

*Another word of warning:* Since we are attempting to establish a hypernormal circulation through the parts, we must realize our effects are upon the vasomotor regulatory system in that region. If we gradually increase the heat, the vasodilatation will be gradual, more complete, and will last much longer. If we turn on a large amount of current immediately, we can produce very marked cramps in the pelvis, adding to the discomfort of the patient, and the vasomotor system cannot react normally. Never turn on the current to full dosage, and always give the maximum available amount of time. Short treatments are almost worthless.

In general pelvic treatments with a large surfaced vaginal electrode and a belt surrounding the pelvis, the current should be sufficient to give the patient a definite sensation of warmth after the treatment has been going about ten minutes. In these cases two or three amperes of current may be used. In the treatment of gonorrhea, however, when we want to get the highest possible temperature in the tissues, in order that the temperature itself may kill the gonococci, it is necessary to

push the dosage to as high an amount as the patient can tolerate. In such treatments small machines are inefficient. When treating the cervical canal with a big machine, there is no evidence of sloughing or destruction of mucous membrane the next day, but if a low voltage machine is used, the mucous membrane will be so coagulated as to make it impossible to treat the patient again for a week or ten days.

It was mentioned above that the dispersing electrode is a belt. We have found from experience that the old technic of using a plate on the abdomen was not as effective as using a three-inch belt of soft metal completely surrounding the pelvis. This may be considered to represent the tire of a wheel. The electrode inserted corresponds to the axle and the current goes back and forth between these two electrodes like the spokes of the wheel. The tissues are most affected where the current is densest, in the region that would correspond to the hub of the wheel, the heat gradually spreading out as along the spokes.

Contraindications for the use of diathermy need not be thoroughly listed, because any gynecologist understands that heat created in a sealed-up cavity, containing pus, will only increase the pain and tend to disseminate the condition. Therefore, such things as acute salpingitis, and other ensaculated collections of pus should not be treated with diathermy. In acute gonorrheal infections, however, diathermy may be used even in pregnant women. We had one such patient at Vanderbilt Clinic who became pregnant just before acquiring gonorrhea without telling us and continued her treatments with the hope that the uterus would empty itself. This, however, did not happen. In Cumberbatch treatments, if the milliamperage is stepped up quickly, patients frequently complain of cramplike pains in the cervix, but in the few patients I have seen who had to be treated though pregnant, no abortion was produced.

In discussing electrotherapy in gynecology, it might be fitting to make mention of two forms of electrical apparatus that are used to create heat in the pelvis. In one the electrical current is used to heat the water within a sac introduced into the vagina. One apparatus has a sac of fixed form and the other has an electrode placed in a condom which is distended by injecting water into it through a special connection. In our hands these machines have not produced effects comparable with diathermy, but the latter type, in which the water can only be heated to 115°, has proved efficient for some conditions wherein diathermy is too irritating. Both these machines heat the tissues by conductive heat, the applicators themselves being hot. This method never can compete with conversive heat created in the tissues by electricity.

For the treatment of gonorrhea, the technic mentioned above has been used. The same wagon wheel action of the current is obtained, but to stress the point again, since the infection is restricted to the



urethra and cervix, I repeat, it is not the physiologic hyperemia that brings about the effects, but it is the result of the actual heat upon the gonococci. Tubal infections cannot be directly heated but have to be treated by the general hyperemia. It is worth noting that we have had a few patients with gonorrhea with definite tubal infection, who, after the infection has cleared up, became pregnant. We can, therefore, expect that the damage done to the tubes was cleared sufficiently for them to function.

The most striking observations we have been able to make from the 350 cases checked up for this report have been in those seemingly operative cases which were given a series of preoperative diathermy treatments. These patients were originally told that they needed to be put on the list for operation, but while waiting for their turn to come, they were sent to our department for pelvic diathermy. Reports on the charts show that pathology found upon operation was a far different picture than the original diagnosis, made when the patient was put on the operation list.

Let me here state regarding this series of cases that every one of them was referred to us definitely and completely diagnosed by the staff of Sloane Hospital. Our department merely treated the patients and referred them back for check-up and eventually for discharge. Conclusions drawn concerning the conditions presented were never made by the staff in the Department of Physical Therapy. Therefore, we feel that our results are worth while because they were not estimated by us but by gynecologists who made the original diagnoses. I wish to record now our thanks for this splendid cooperation.

It is to be regretted that we cannot have more specific infections to treat, but the problem of hospitalization for these patients if they became acutely sick could not be handled in a clean hospital. We, therefore, were restricted in the number that could be given ambulatory treatments, and results obtained are not comparable to my own experience in private practice, because these patients had to go on with their occupations and, frequently, had to skip treatments because of lack of funds to pay for them.

In three patients with gonorrheal arthritis who were admitted to the wards with another diagnosis, and the true etiology later discovered, our treatment of the pelvic infection while the patients were in bed showed its great effectiveness, in that the pelvic infection was entirely cleared up in less than ten treatments. One patient with suppurative arthritis of the ankle that was opened in the emergency room and admitted, showed positive smears from the wound; after four pelvic treatments, these smears failed to show gonococci. Her pelvic infection was cleared up in nine treatments and remained so over a period of four monthly examinations.

Another patient with gonorrheal arthritis of the wrist, latently diagnosed, started treatment in bed, continuing in the clinic, and though she has a very marked, severe swelling of the right wrist, she has now resumed her occupation as a concert pianist.

In all cases of gonorrhea we advise douches after the first 3 or 4 visits and also give the patients a course of ultraviolet baths. We do not stop with the first negative smears but keep the patients under continuous twice weekly treatments until three sets of negative smears have been reported. Some of the patients in our series were discharged by the staff of the Sloane Hospital because of clinical appearance after only two negative smears, but we classified these as "incomplete." All our "cleared" cases had three or more negatives.

The gonorrheal cases that we have been able to get into our department from the Sloane Clinic have numbered 30, five of which are still having treatment. We have been able to follow 12 patients until they could be declared totally cleared, which means, as stated above, that they have had three to six or more slides that were negative for gonococci, had no symptoms of any condition, no discharge, and were reported as clinically cleared up after pelvic examination by Sloane Clinic. To date there are five patients who have had only two negative slides but who were pronounced entirely cleared up and cured by the Sloane Clinic. One of these became pregnant and had a healthy child. Eight other patients have likewise been discharged by Sloane after only two sets of negative slides, but recorded as improved and, no pathology; on their charts.

There have been 280 patients treated for nongonorrheal conditions in our department, of which 40 are now under treatment. Of the 240 discharged, 107 had no final discharge note on their charts but were told by the Sloane doctors that they did not need any more diathermy. Of the remaining 173 cases, the recorded final examinations show that 61 patients did not have any pelvic pathology and 116 were so improved as to be able to be discharged by the clinic.

These nonspecific cases have represented practically every condition that can occur in the pelvis except malignancies and cysts. A great many of them were postoperative cases, where operation was necessary for some acute inflammatory condition. I shall not try to go into any list of specific conditions that can be improved by diathermy, but the patients that can be treated are practically all those with inflammation that do not require immediate surgery. There are many conditions that were so improved that subsequent operation was less radical.

The indication for diathermy in all pelvic conditions is whether improved circulation will help, but I do not believe that diathermy alone is always the complete treatment. It is sometimes necessary to electrically stimulate the uterus, as in an infantile organ, or to stimulate the entire pelvic contents to promote drainage. This is done with forms

of electricity other than high frequency, but I shall not go into these cases because the subject of this paper is the use of diathermy alone. We, in our department, do not believe that diathermy is a cure-all in any sense, but is just a means with which to attempt to restore normal circulation. This, of course, may also happen over a period of months without any treatment, but, as a member of the clinic staff stated, "diathermy seems to do in a few weeks what it takes Nature years to accomplish."

730 FIFTH AVENUE

## TRANSVERSE CERVICAL CESAREAN SECTION\*

A CRITICAL ANALYSIS OF ONE HUNDRED AND FIFTY CONSECUTIVE CASES

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CESAREAN section is an important contributor to maternal mortality. It has been shown by the Federal Bureau of Vital Statistics that deaths from this operation have mounted steadily during the past ten years. Moreover, as the incidence of abdominal deliveries seems to be increasing, we may expect these figures to become even more tragic during the next decade.

Two means of preventing this are suggested. First, by reducing the actual number of sections performed. Unquestionably a cesarean section is often resorted to, because it seems to be an easy solution to a difficult obstetric problem which could be solved more conservatively if proper knowledge and training in pelvic deliveries were available. But this involves that chimerical ideal of all who are interested in lowering maternal mortality, better obstetric education, pregraduate and postgraduate, and is beyond the scope of this paper.

The second method of decreasing deaths from cesarean section is by encouraging the more general adoption of the safest type of this operation. In a summary of 12 series of classical and cervical cesarean sections, collected from various parts of the country by Skeel and Jordan in 1932,<sup>†</sup> it was found that 3,468 classical sections were fatal in 192 cases (5.2 per cent) and 2,753 cases of cervical section in 70 cases (2.5 per cent).

The laparotrachelotomies show a mortality less than one-half the rate for the fundal operation. These figures become more impressive when we consider that in many instances the cervical section was chosen because the patient was in the "potentially infected" group.

The favorable aspects of the various types of laparotrachelotomy have been summarized briefly as follows: a definitely lower mortal-

\*Read at a Meeting of the Boston Obstetrical Society, November 20, 1934.

†Am. J. Obst. and Gynec. 23: 172, 1932.

ity; a lower morbidity and smoother postoperative course; better healing of the uterine incision with less possibility of subsequent rupture; a minimum of intraperitoneal adhesions and by no means least important, because it lowers fetal mortality also, by lessening the number of destructive high forceps deliveries, applicability to cases after a trial labor or with ruptured membranes.

The low transverse section first described by Phaneuf in 1927, commends itself particularly because the uterine incision may always be confined to the lower segment. Before adopting the transverse incision it was sometimes found necessary in delivering a large fetal head, to extend the longitudinal incision into the body of the uterus. Also, when the operation was performed before term, the lower segment was found to be too short to permit the easy extraction of the fetus. This made it necessary either to perform an abdominal accouchement forcé or to extend the incision into the corpus uteri. This resulted in damage, often fatal, to the premature baby; or a failure to secure all the advantages that accrue from keeping the uterine incision below the isthmus. These difficulties are avoided by the transverse incision, as it may be curved with its convexity toward the symphysis, making an ample flap through which a large baby may be extracted with comparative ease. Another point in favor of the transverse incision is that less separation of the bladder from the cervix is required.

To stimulate further interest in this operation and to encourage its more general adoption, the following analysis of 150\* consecutive transverse cesarean sections performed by me is presented. Six of these were ward patients, treated at St. Mary's Hospital, Dorchester. The remaining 144 were from my private and consultation practice and were attended in 14 hospitals in, or adjacent to, Boston.

#### INDICATIONS

The reasons for abdominal delivery are outlined in Table I. In many patients, two or more abnormalities were evident, but the most important one is recorded. As usual, cephalopelvic disproportion leads the list with 43.3 per cent. As many of the repeat operations were in this category, the actual incidence was much higher.

In the previous section group, 6 had the classical operation, 6 had both classical and cervical sections, and 26 had laparotrachelotomies. Of the latter, 18 had 2, 7 had 3, and 3 had 4 cesareans. There was a notable absence of adhesions in the last group. The bladder could, as a rule, be again separated from the lower uterine segment by finger dissection. Rarely a fibrous band required incision.

Although in many of the repeat cases at term the lower segment was found to be very thin, no weak scars were found. On the contrary, the repair had been so complete, in most instances it was not possible to determine the site of the previous incision.

\*Since submitting this article for publication I have performed 14 additional transverse cervical cesarean sections, making a total of 164 cases without maternal mortality and with no additional fetal mortality.

Patients with preeclamptic toxemia and chronic nephritis were sectioned only after a thorough trial of efficient medical treatment failed to control the condition. The two eclamptics were primiparas in good condition, not in labor, with large babies.

TABLE I. INDICATIONS

	CASES	PER CENT
Cephalopelvic disproportion	65	43.3
Previous cesarean	38	25.3
Eclampsia	2	1.3
Other toxemias	19	12.6
Abruptio placentae	2	1.3
Placenta previa	11	7.3
Cardiac disease	3	2.0
Cervical stenosis	4	2.6
Myomectomy (during pregnancy)	2	1.3
Obstructing fibroid	1	0.6
Complete perineal repair	2	1.3
Old pelvic fracture (obstructed outlet)	1	0.6

Hemorrhage resulted from abruptio placentae in two cases. One had a typical uteroplacental apoplexy with extensive hemorrhagic infiltration of the myometrium which made hysterectomy necessary.

Placenta previa was judged to be complete in 5 parturients and partial in 6. Two of the complete previas occurred in multiparas, while all the remainder were primiparas. Transfusion of 500 c.c. of blood by the citrate method was necessary in 2 cases, before operation. The particular advantage of laparotrachelotomy over the classical section in placenta previa was evident in 3 cases. In one a tongue of placental tissue extended into the cervical canal. This was easily visualized and withdrawn, but this would probably not have been possible with a fundal incision. The other two patients showed large uteroplacental sinuses which were closed with x-shaped sutures. These sinuses continued to bleed freely after the fundus contracted, and clearly demonstrated why postpartum hemorrhage frequently follows placenta previa.

All three cardiac patients had severe mitral stenosis with regurgitation. One decompensated at the fifth month, but recovered and was sectioned at eight and one-half months, under local anesthesia.

The two patients requiring myomectomy during pregnancy were elderly primiparas, who were operated upon after a thorough trial of conservative treatment failed to control the symptoms of acute degeneration of the fibroid, viz, extreme pain, rise of temperature and flowing. One gravida was three and one-half and the other four months pregnant. At term both had large babies and in one the pelvic outlet was contracted.

The case of fetal distress occurred in a normal primipara of thirty-five, married five years, who was seen in consultation because the fetal heart was failing. Labor had been in progress for six hours. There was no disproportion, the position was left anterior, with the vertex dipping into the pelvic inlet, not engaged. The membranes were intact, the cervix about one-half effaced and two fingers dilated. The fetal heart was 144 on admission and had dropped during the last three hours to 112, with slight irregularity. On section, the cord was found to be tightly coiled around the baby's neck 3 times and the amniotic sac contained a large amount of meconium. Following delivery the baby did very well.

## INTRAVENOUS PITUITARY EXTRACT

In the last 126 cases of the series 0.5 c.c. of pituitary extract, diluted with 4 c.c. of warm salt solution, was instilled slowly into a vein in the elbow as soon as the fetal head was delivered. This causes a prompt, firm contraction of the fundus uteri. The advantages of this are threefold: conservation of the patient's blood, spontaneous separation of the placenta, and a clearer operative field. If given *slowly*, in the above dilution, pituitary shock does not occur. Uterine tamponade was never considered necessary and no patient in the series developed postpartum hemorrhage.

## DURATION OF PREGNANCY

Table II shows the length of pregnancy. All patients operated upon before the ninth lunar month were either toxemias or cardiacs.

TABLE II

Over 10 lunar months	14
9½ lunar months	119
9 lunar months	7
8½ lunar months	7
8 lunar months	2
7½ lunar months	1
	<hr/> 150

## DURATION OF LABOR

The operation was performed after the onset of labor on 84 patients, or 56 per cent. The remaining 66, or 44 per cent, were not in labor.

Table III shows the length of labor prior to operation.

TABLE III

HOURS	CASES	PER CENT
1 to 4	4	2.6
4 to 8	5	3.3
8 to 12	11	7.3
12 to 24	45	30.0
24 to 36	11	7.3
36 to 48	4	2.6
48 to 60	3	2.0
60 to 72	1	0.6
	<hr/> 84	

The patient with the longest duration of labor was seen in consultation sixty-eight hours after the onset of pains. She was a primipara with a funnel pelvis and a very large baby presenting by the breech. The cervix was fully dilated and the membranes intact. The baby weighed 10 pounds 4 ounces. The mother made an uneventful recovery, and left the hospital on the thirteenth day.

## MEMBRANES

Patients with intact membranes at the time of operation numbered 113, or 75.3 per cent. In 31, or 20.6 per cent, rupture had occurred and in the remaining 6, the condition of the membranes was doubtful.

One patient, a duopara aged twenty-seven, had an escape of fluid for five days. She had a justminor pelvis with a large baby, and a history of a long first labor

terminated by high forceps delivery of a stillborn baby. A third-degree laceration of the perineum resulted, which had been successfully repaired six months later. Her temperature was 99.4°. A porro operation was considered, but the uterus was not removed and the patient made a good recovery except for a rise of temperature to 102.2° on the second day.

#### MORBIDITY

A smooth, comfortable convalescence, with very little nausea, vomiting, or distention may usually be expected after the low transverse cesarean. Several patients in this series had one or more vaginal examinations and in four an attempt at delivery from below had been made. The last 36 patients of the series received 0.5 c.c. of pitressin every four hours for 5 doses. This seems to be helpful in stimulating peristalsis and in promoting normal bladder function.

Table IV indicates the temperatures. Fifty-nine, or 59.5 per cent had a rise of temperature over 100, persisting for twenty-four hours or longer.

TABLE IV. TEMPERATURES

DEGREES F.	CASES	PER CENT
98.6 to 100	91	60.6
100 to 101	32	21.3
101 to 102	19	12.6
102 to 103	6	4.0
103 to 104	2	1.3

Most of the elevated temperatures were of the "reaction type" and subsided to normal after three days. A definite cause for fever was demonstrable in 27 cases (Table V).

TABLE V. COMPLICATIONS OF PUERPERIUM

	CASES
Endometritis	8
Bronchitis	2
Phlebitis	5
Pneumonia (lobar)	2
Abscess of buttock (Mg. So 4 injection)	1
Parametritis	1
Wound infection	5
Pulmonary embolism	1

#### PORRO OPERATIONS

Two hysterectomies were performed. The first was a quadripara aged 36, nine months pregnant. Her physician had been treating a mild toxemia for 4 weeks. She suddenly was seized with severe abdominal pain and flowing. Examination revealed the characteristic symptoms of severe abruptio placentae. Labor had not started and there was a steady flow of blood from an undilated cervix. On section the myometrium was so friable and infiltrated with blood that it was necessary to do almost a complete hysterectomy to secure cervical tissue which would hold sutures. A live baby was secured and the patient recovered uneventfully. The other, a duopara, aged 34, had a large cervical fibroid, which almost filled the pelvis.

#### HOSPITAL STAY

Table VI lists the number of days spent in the hospital.

The patient who remained seventy-eight days was a repeat section, who entered the hospital with an unrecognized respiratory infection. After ether anesthesia,

lobar pneumonia developed, followed by bilateral femoral phlebitis. It is noteworthy that 127 patients, or 84.6 per cent left the hospital within sixteen days.

TABLE VI. HOSPITAL STAY

DAYS	PATIENTS	DAYS	PATIENTS
11	3	17	13
12	24	18	4
13	33	20	2
14	39	24	3
15	16	78	1
16	12		

127, or 84.6%      23, or 15.3%

## ANESTHESIA

Table VII shows the types of anesthesia used. Spinal anesthesia was usually employed when pulmonary complications were present. Local anesthesia (novocaine solution 0.05 per cent, with 3 drops adrenalin solution, 1-1000 to the ounce), with preliminary barbiturates, was used in the severe toxemic and cardiac patients. In these, a small amount of  $N_2O$  and O was administered while the baby was being extracted from the uterus. The gas was then removed and morphine sulphate gr.  $\frac{1}{4}$  was given subcutaneously.

TABLE VII. ANESTHESIA

$N_2O$ and ether	97
Spinal anesthesia	7
Local anesthesia	19
Avertin with ether	19
Avertin with $N_2O$	8
	<hr/> 150

Avertin, as a basal anesthesia has proved to be very satisfactory, in the latter cases of the series; when no contraindication exists it is now the anesthesia of choice. It appears to have no effect on the baby.

## MORTALITY

There were no maternal deaths. One baby was stillborn and seven babies died after delivery, a neonatal mortality of 5.3 per cent.

1. Primipara, aged twenty-five, seen in consultation after an attempt at high forceps by family physician. Justominor pelvis with large baby. Fetal heart 134 and regular. After delivery, baby showed a depression from forceps over left parietal bone and died in fourteen hours from intracranial hemorrhage.

2. Primipara, aged twenty-eight. Severe preeclamptic toxemia. Local anesthesia. Premature (eight months), toxic baby. Died third day.

3. Primipara, aged twenty-nine. Complete placenta previa. Anencephalic monster.

4. Primipara, aged thirty. Severe preeclamptic toxemia. Local anesthesia. Premature (seven and one-half months) baby. Died second day.

5. Primipara, aged thirty-four. Severe preeclamptic toxemia. Local anesthesia. Premature (eight months) baby. Died second day.

6. Duopara, aged thirty-two. Repeat section at term. Seven-pound 12-ounce baby. Atelectasis pulmonum. Died third day.

7. Tertipara, aged thirty-four. Repeat section at term. Eight-pound 2-ounce baby. Cerebral hemorrhage; died second day.



8. Tertipara, aged thirty-nine. Two previous sections for cephalopelvic disproportion; first classical, other transverse cervical. Moderate preeclamptic toxemia. Two weeks before term, cessation of fetal movements with onset of labor twenty-four hours later. No fetal heart heard. Large stillborn macerated fetus. Placenta showed extensive infarction.

#### CONCLUSION

1. Cesarean section mortality is steadily increasing in the Registration Area of the United States.

2. The author believes that more general adoption of the cervical operation would materially decrease the number of these deaths.

3. An analytical review of 150 consecutive transverse laparotracheotomies is presented with no maternal mortality, one stillbirth and seven neonatal deaths.

524 COMMONWEALTH AVENUE

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### A NEW METHOD FOR MEASURING THE BLOOD LOSS DURING THE THIRD STAGE OF LABOR

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THE purpose of this paper is primarily to introduce a new method of accurately measuring blood loss during the third stage of labor. In a subsequent paper the results obtained with the use of the apparatus will be presented.

It is surprising to find so few procedures suggested for measuring blood loss at the time of delivery. In the usual method now in use, an attempt is made to collect the blood in a receptacle and later to measure it in a graduated glass cylinder. In 1904, Ahlfeld, who was one of the first to measure blood loss, suggested a unique method with which he was able to obtain data relating to blood loss before, during, and after the expression of the placenta.

Ahlfeld's specially constructed bed had a 22 cm. opening through the mattress into which a metal funnel was placed. A graduated cylinder on the floor served as the receptacle for the blood. A pillow was then placed over the opening and the patient's buttocks allowed to rest over this. Following delivery of the baby the pillow was replaced by a sheet with an opening over the funnel. In this way the amniotic fluid was eliminated. The blood collected in the cylinder was watched by an assistant who could warn the operator if there was an excessive amount of blood loss. Deductions for urine were also made by the assistant. As a rule, however, the patients were catheterized immediately after delivery to avoid this discrepancy. The placenta

itself and the placental blood were caught in a porcelain dish. During this procedure the assistant changed the graduated cylinder so as to obtain the loss after the expression of the placenta. The loss in each of these containers and the total were then recorded. Although this method would not be suitable for the present-day delivery, it furnished him with accurate determinations for the three phases of the third stage.

In 1919 Williams reported a series of 1,000 full-term spontaneous deliveries in which the blood loss was measured by his own method. His patients were placed on a sterile douche pan after delivery of the baby and the blood collected in the pan. After completion of the third stage the blood was measured in a graduated cylinder and recorded as the total loss.

Since then several modifications of his method have been in use. Recently the subject was covered by Calkins, who in 1929 presented a study of 853 cases with the blood loss measured by his own technic. His method is as follows: "At the first show of blood, after delivery of the child, a sterile hand basin is placed against the perineum between the vulva and the anus. The placenta and associated blood are caught in this basin. The basin is held in place until the active bleeding has been controlled. The blood in the pan is then measured in a graduate and is labeled the measured loss. In the majority of cases there is other bleeding previous to the placental stage, either from laceration or episiotomy, or subsequent to it from imperfect contraction of the uterus, injuries to the birth canal, etc. This amount is estimated, care being taken not to underestimate it. This second portion is called the estimated loss. While, theoretically, the method employed in arriving at this latter amount is subject to error, it is believed to be accurate to 25 c.c. on the average. It was selected in preference to the more accurate method of Williams because of the desire to separate the placental stage blood from other bleeding, as different factors might be involved in the two types. The sum of the measured loss and the estimated loss equals the total loss."

It would appear, therefore, that any satisfactory method should have certain prerequisites, as follows:

1. The method should not interfere with the sterile technic so essential to reduce puerperal morbidity and infection.
2. It should not interfere with operative procedures, such as operative deliveries, manual removal of placentas, repairs of perineal and cervical lacerations.
3. It should permit the accurate determination of the blood loss before, during, and after the expression of the placenta.
4. It should permit the operator to know at any one time how much blood loss the patient has sustained, so that he may be guided in the management of the third stage.
5. It should be accurate, without personal estimation of blood loss, so that data throughout the country can be compared.

The method which is now in use routinely in the Woman's Clinic of the New York Hospital has been developed to meet these requirements. The apparatus has been developed with the cooperation of the Engineering Department of the New York Hospital, and I am most grateful to Dr. H. J. Stander for placing these facilities at my disposal. The cooperation and suggestions of other members of the staff of the Woman's Clinic have been most valuable during the experimental period.

There are two principles involved in this method of measuring the blood loss. First, the blood is collected throughout the entire duration of the third stage in such a manner that the amniotic fluid and other cleansing solutions can be easily eliminated. Second, the loss is immediately registered on a manometer attached to the table and visible to the operator.

The apparatus itself consists of four different parts. Fig. 1 is a diagrammatic sketch of the table and apparatus, and in Fig. 2 the various parts of the apparatus

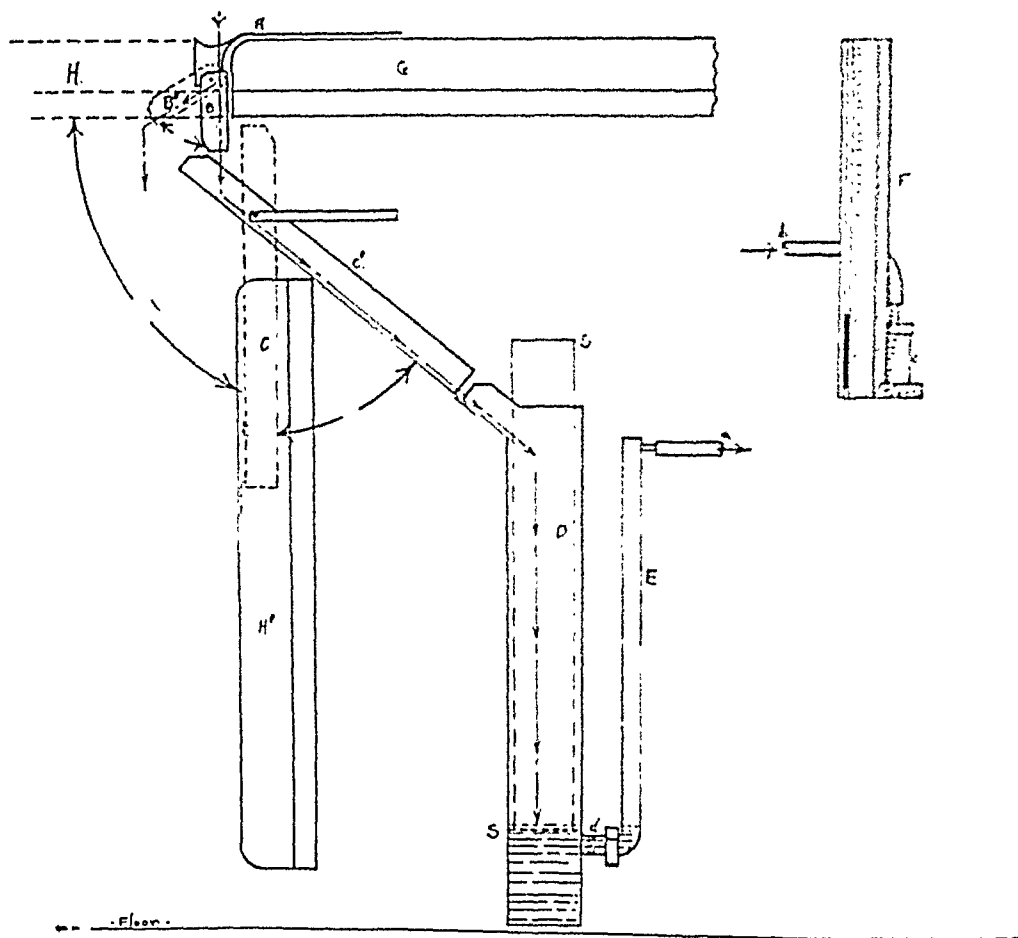


Fig. 1.—Diagrammatic sketch of apparatus and delivery table.

are pictured. The tables which are used in the Woman's Clinic are so constructed that the lower half of the table is lowered when the patient is ready for delivery. In the diagram the table is represented by the letters *G* and *H*. When the table is lowered *H* comes into position *H'*. The patient is then placed in stirrups and cleaned as per routine. A sterile Hampton pad is then placed under the buttocks. The pan *A-B* is placed under the patient and the drapes applied. This pan is of flat Monel metal and contains the adjustable trough *B*, as shown in the photograph. When the trough *B* is brought into position *B'* the amniotic fluid and the cleansing solutions are eliminated from the apparatus and drop into the waste bucket on the floor. This pan is the only part of the apparatus which is sterile and with which

the operator comes in contact. It is of such size that it can be sterilized with the instruments. The trough is left in position *B'* until after the delivery of the baby and until the flow of amniotic fluid is completed. It is then lowered to position *B* and the blood collects in the apparatus. If solutions are used to wash the perineum before repairing lacerations, the trough is left in position *B'* during the cleansing. The relative position of this trough is shown in Fig. 3.

The blood from this pan is directed through the trough *C* into the cylinder *D*. This is also of Monel metal. Because of the nature of our tables it is suspended

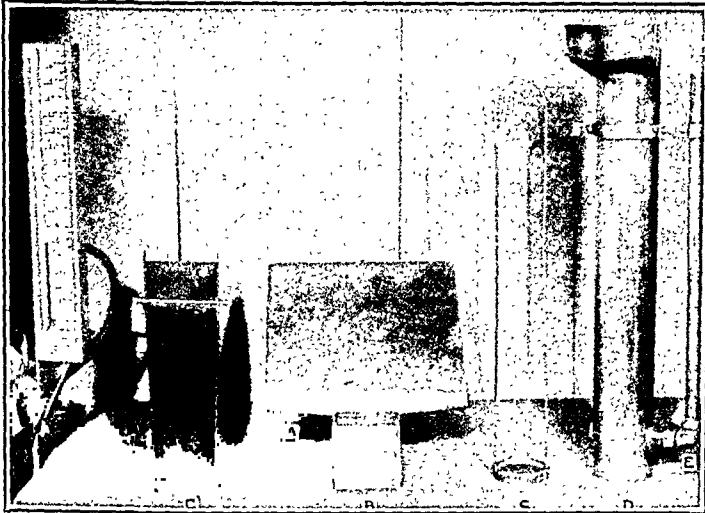


Fig. 2.—Photograph of the various parts of the apparatus.

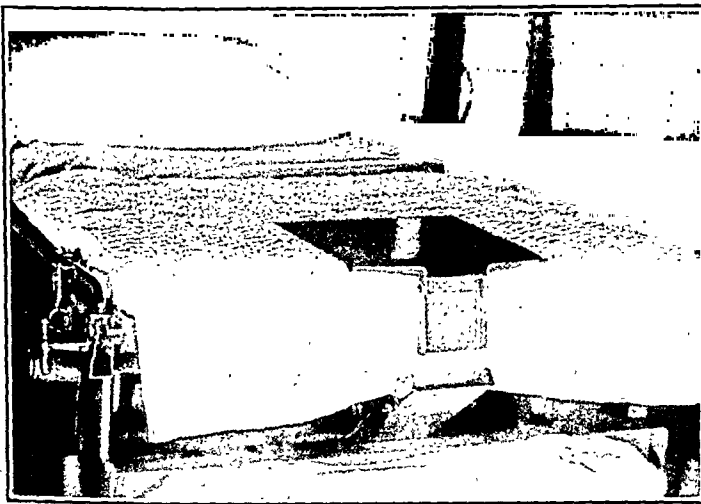


Fig. 3.—Photograph illustrating position of the trough when the blood is being collected in the apparatus.

from the table by a cross bar and rests in position *C* before the table is lowered, as shown in Fig. 4. As table *H* is lowered to position *H'*, the trough *C* is raised to position *C'*. It is easily removed, cleaned, and replaced after each delivery. With other types of delivery tables, particularly those which break into two sections, the trough *C* can remain in permanent position *C'*.

The double cylinder *D-E*, shown in Figs. 1, 2, and 4, is also attached to the table by a cross bar so that it can be easily removed and cleaned. It is constructed of brass so as to resist erosion. The two cylinders are connected at point *d*, which con-

tains a metal screen to prevent blood clots from entering cylinder *E*. In addition the circular screen *S*, shown in Fig. 2, facilitates the cleaning of the apparatus. After the cylinder is cleaned, it is filled with water to a level above *d*. The exact measurement of the water is not necessary except for purposes of checking the apparatus after delivery. We use 400 c.c. of water so that the total amount of fluid in the cylinder after delivery minus 400 c.c. should give you the amount recorded on the manometer. After the cylinder is placed in position under the table, the rubber tubing connecting it with the manometer *F* is attached at point *a*. This makes a closed system between the water level in *E* and the manometer. When the level in *D* rises the increased pressure in *E* is recorded in cubic centimeters on the manometer. The manometer, therefore, registers the increase in pressure in the cylinder *E*. This pressure is created by the increase in height of the column of blood in *D*. Since there are no mechanical parts involved in this method, the readings are not subject to error.

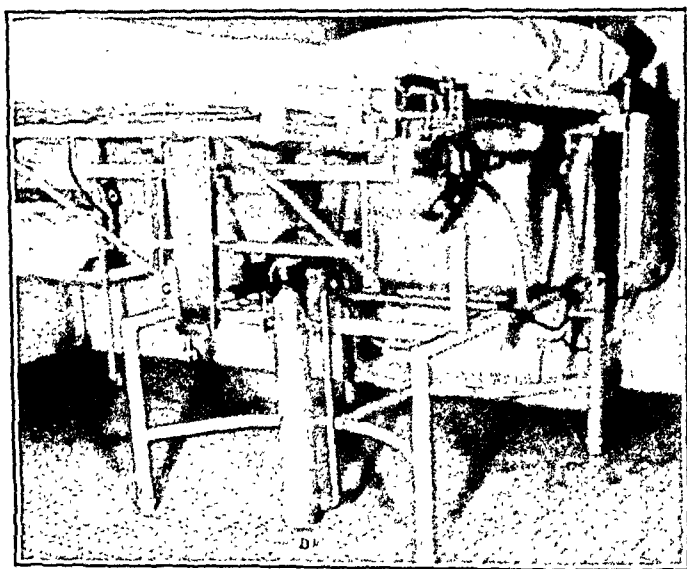


Fig. 4.—Attachment of the apparatus to the delivery table and the position of the manometer when not in use.

The manometer is attached to the head of the table on a sliding bar so that it can be lowered under the table when not in use, as shown in Fig. 4. The scale, illustrated in Fig. 5, is large enough to permit readings of 5 c.c. of blood loss. Each 100 c.c. loss equals 2 cm. on the scale. Regardless of the amount of water placed in the cylinder *D*, the reading is always zero when the rubber tubing is connected.

Because of the technicality of the above description, it seems necessary to restate that it is only necessary at the time of delivery for the operator to insert the sterile pan *A-B* under the buttocks and to adjust the trough *B* after delivery. The rest of the apparatus is cleaned and attached to the table by the orderly after each delivery so that it is always ready for the next delivery.

The apparatus offers a much more simple and accurate method of measuring the blood loss during the third stage. It measures the loss while the operator is repairing cervical or perineal lacerations. Any operative procedure may be carried out without interference. The trough in *B'* position does not interfere with forceps

delivery or version and extraction. It permits manual removal of the placenta with accurate determination of the blood loss. The placenta alone is caught in a basin and the blood allowed to flow into the apparatus.

By taking readings during the three phases of the third stage, the loss before, during, and after the expression of the placenta is determined. By knowing the exact loss at any one time, the operator is guided in the management of the third stage. Manual removal of the placenta can be carried out when it is obvious that the blood loss is becoming abnormal, as will be shown in a subsequent analytical study of the third stage.

It has proved of even greater value in cases of vaginal bleeding during the last trimester of pregnancy where vaginal examination is resorted to. The bleeding in cases of placenta previa during examination, insertion of Voorhees' bag, or Braxton Hicks version can be determined. Measurement of the amount of amniotic fluid can,

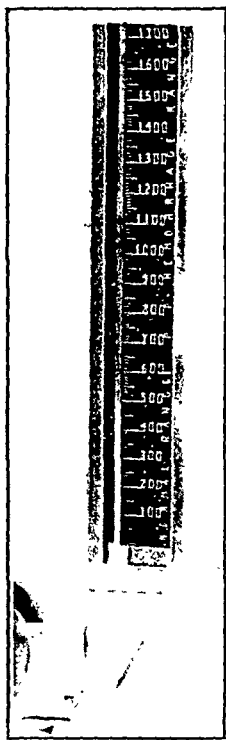


Fig. 5.—Manometer in position for use.

of course, also be made. For experimental purposes large quantities of blood can be collected, as normal saline or citrated solutions can be used to replace the water in the cylinder.

I feel quite certain that this method of determining the blood loss during the third stage of labor removes the personal equation of estimation which undoubtedly accounts for the wide variation in the blood losses reported from the various clinics. Our studies thus far on 500 consecutive deliveries have shown that estimations are inaccurate and that there is a tendency to overestimate losses below 150 c.c. and to underestimate losses above 400 c.c. The real factors responsible for excessive blood loss can be determined only when reports from the various clinics can be studied on a comparative basis.

#### SUMMARY

A new method of measuring the blood loss during the third stage of labor is presented. The apparatus is described in detail so that

comparative figures might be obtained from the various clinics of the country. It permits accurate determination of the blood loss throughout the entire period of the third stage. The fact that estimations of blood loss at the time of delivery are misleading cannot be over-emphasized.

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## AN ANALYSIS OF 1,772 ABORTIONS AND MISCARRIAGES WITH A CONSIDERATION OF TREATMENT AND PREVENTION\*

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THIS study is based upon an analysis of 1,772 consecutive case records for the years 1929 to 1932 inclusive, at the Boston City Hospital. The term "abortion" is used in the sense given in DeLee's textbook of obstetrics, which is, extrusion of the products of conception at any time up to the twenty-sixth to twenty-eighth week of pregnancy, or the time of viability. This includes of course all cases of miscarriage in the usual understanding of the term. In each case included in the series either the pathologic report showed the presence of pregnancy, or the operator reported gross placental tissue present. The latter criterion, of course, is open to some error. Taken in connection with other facts in each case, however, such as the pelvic examination and history it is likely that the errors in diagnosis are not sufficiently great to be significant. The conventional 100.4° of temperature is used to denote a septic case, and anyone reaching or exceeding this level is so considered. Any temperature of 99° or over is considered febrile. A direct correlation has been found between the length of stay in the hospital, and the duration of the temperature. The latter is considered to be the best guide to the clinical course available, and it has been used as such. The appellation "dilatation and curettage" is used somewhat loosely to denote active intervention. Actually, probably very few of the patients required dilatation. A small number under this heading had simply manual extraction. Others had a finger curettage or removal with placental forceps. The majority had a combination of the latter with curettage.

\*Read in part at the Clinical Congress of the American College of Surgeons at Boston, October 16, 1934.

The operations were done by the senior house officer. These men move up every four months, so the surgery has been done by a considerable group. The usual treatment of incomplete bleeding cases is as follows: An ampule of pituitrin and one of ergot is given on admission, and the latter is repeated for three to six doses if necessary. Hourly pulse and temperature readings with careful observation for bleeding are ordered. Markedly septic cases are put in high Fowler's position, and an ice bag was applied to the abdomen. Sedatives are given as indicated. Briskly hemorrhaging cases have the uterus emptied at once, as well as those with continued bleeding and contractions where it is obvious that the pregnancy will not continue. Bled out cases are transfused prior to operation whenever possible.

As for the actual patients: in common with other published series, it is found that the majority were married women, 91 per cent in fact. Nine per cent were single. The average number of children per case is 2.9. There was a history of previous abortion in 650 cases, and 256 cases admitted mechanical interference prior to admission. Fifty-four attempted medical induction. The average duration of pregnancy was 2.9 months. Of the 1,772 cases, 313 or 18 per cent were septic on admission, 1,481 were operated upon. The gross mortality for the series is 1.7 per cent. In other series published in recent years, the mortality runs from 0.88 per cent (Watkins) to 9 per cent (Witherspoon) the latter for operated cases only. Taussig's very large series in this country had a 2.1 per cent mortality.

There is one type of case which is of interest. It has been noted by E. B. Pearce, writing in the *Journal of Obstetrics and Gynecology of the British Empire*. This is the patient whose temperature drops suddenly, within a day or two from a high level to normal and remains normal. This type of reaction resembles very much the crisis of pneumonia. It has no apparent relation to either dilatation and curettage or spontaneous abortion in the present series. There were 124 such cases.

Unfortunately it has been found impossible to compare directly the group of cases having dilatation and curettage with those not operated upon, for the following reasons: First, the dilatation and curettage had a mortality rate of 0.9 per cent while the nondilatation and curettage had 6.2 per cent mortality. Second: 16 per cent of the dilatation and curettage group were septic on admission, while 26 per cent of the nondilatation and curettage were septic on admission. From these two facts, it is apparent that the sicker patients were treated conservatively. There is thus a definite division, clinically, within the group of septic cases.

One valid comparison can be made, however, to show the effect of surgical intervention upon patients with a septic temperature. If the



group receiving dilatation and curettage is divided into septic and nonseptic on admission, and compared for duration of temperature, it is found that those who were septic had an average of four days of temperature, while those who were not septic had 3.3 days of temperature.

If, as so many authors claim, with considerable heat and fervor, it is always dangerous and unsurgical to invade the septic endometrium, we would not expect to find, as we do here, that both operative and nonoperative septic cases became afebrile in so nearly the same short period of time. It would seem rather, that in properly selected cases, a high temperature, denoting sepsis, is not invariably a contraindication to prompt and judicious emptying of the uterus.

The sociologic aspect of these cases though not susceptible to statistical treatment is, nevertheless, interesting. It is in the large group of induced abortions that hope lies of reducing the numbers of these cases. It is a striking fact that over three hundred of these mothers admitted attempts to induce abortions on themselves. Obviously a great many more must have done so, but were unwilling to admit the fact. There is no need to dwell on the grave social consequences resulting from the loss of a mother to a home in those cases having a fatal outcome, or on the after-effects of complicated septic cases. These are self-evident. A word may be said, however, on the cost of caring for these cases. We do not know how many of the whole series of 1,772 cases were actually induced, and therefore potentially preventable. The total expense is worth considering, however. The average cost of caring for a ward patient during the year 1930 was \$5.64 per day, according to the sixty-seventh annual report of the hospital. These 1,772 patients stayed a total of 13,746 days, making a total cost of \$77,527.44. A not inconsiderable sum should be added to this to cover the cost of operation in the 1,481 patients so treated. There is no way of arriving at this figure since the services of the operator and anesthetist, being house officers, are free except for board and room furnished by the hospital.

Until recently there has been no means of getting at the seat of the trouble by preventing the occurrence of any considerable number of the self-induced group. Knowledge is at hand, however, and awaits only the organization of the large maternity centers of the country, to bring about a great reduction in the incidence of induced abortion. Specifically, it is the practical application of the Ogino-Knaus law of alternating sterility and fertility in the menstrual cycle.

That there is a public demand for information in regard to birth spacing and limitation is shown by the survey conducted under the auspices of the Johns Hopkins School of Public Health, by Pearl, and reported in *Human Biology* for May, 1934.

## SUMMARY AND CONCLUSIONS

1. There have been 1,772 consecutive case records of abortions and miscarriages on a large metropolitan service studied for the years 1929 to 1932 inclusive.
2. The total cost of these patients to the hospital was considerably in excess of \$77,527.44.
3. Ninety-one per cent were married women.
4. The mortality was 1.7 per cent.
5. There is little if any difference in duration of morbidity between the septic and nonseptic patients who were operated upon.
6. Three hundred and ten individuals admitted attempts at induction.
7. Evidence has been presented from the literature to show that means are at hand to regulate many of these unwanted pregnancies by proper organization and instruction at the large maternity centers of the country.
8. The method under consideration does not violate any religious principles or esthetic considerations.
9. The technical accuracy of the Ogino-Knaus method has been established; its social efficacy can be determined only by an adequate trial.

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*Staehler, F.*: The Symptom-Free Time in Uterine Carcinoma, Arch. f. Gynäk. 153: 561, 1933.

In a series of 200 carcinomas of the uterus, the author found that the average period without symptoms was 2.7 months. It was 4.75 months in seven patients in whom the uterine carcinoma was accidentally found. In twenty-five (1 out of 8) the carcinoma was inoperable even though the patient sought advice and treatment as early as possible, since the carcinoma had been present but latent for 4.5 months. There is apparently no relationship between the age of the patient and the duration of the latent period.

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# FETAL CEPHALOMETRY IN UTERO AND THE DETERMINATION OF FETAL MATURITY

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IN 1930<sup>1, 2</sup> I published two papers relating to the use of roentgenometry in determining the occipitofrontal diameter of the fetal head in utero. At that time I pointed out that information thus obtained served as an index to fetal maturity and also as an index of the probable biparietal diameter. Since that time the usefulness of fetal cephalometry in utero for determining fetal maturity has been emphasized by other writers, notably Jarcho<sup>3</sup> and Clifford.<sup>4</sup>

The present communication deals with further experience with the method and emphasizes again the clinical value of the procedure. Our method is an adaptation of the grid method of roentgen pelvimetry, and as I pointed out in my first communications it is accurate for clinical purposes.

To quote.—“In this method, the plane in which any diameter lies must be identified and its distance above the sensitive plate measured, in order that the amount of divergence of the roentgen rays may be corrected. In the case of the occipitofrontal diameter, the forehead and occiput must be palpated through the abdominal wall, and their respective distances from the sensitive plate measured. It will be remembered by those familiar with obstetric palpation that the identification of these two portions of the fetal head in the latter weeks of pregnancy is readily accomplished in the majority of cases. The exposure is made with the tube or target at a thirty-six-inch distance, centering as nearly as possible over the parietal region of the fetal head. Following the exposure, the patient is removed from the table, the target and exposed plate remaining in situ. A lead grid with perforations exactly 1 cm. apart is now introduced in the plane previously occupied by the occipitofrontal diameter of the fetal head, and a flash exposure is made on the previously exposed plate. Upon development, not only will the outline of the fetal skull be seen, but also a series of dots representing the centimeter distance. Calculation of the occipitofrontal diameter is readily accomplished by calipers.

“It is obvious for the sake of accuracy that the fetal head should be movable at the superior strait. In other words, if the head is deeply and fixedly engaged in either the right or left oblique diameters of the superior strait, the shadow projected on the sensitive plate will be somewhat distorted. Experience has shown, however, that in practically all cases where a knowledge of fetal maturity is desired, no such deep engagement is present, and the fetal forehead and occiput are readily palpable through the abdominal wall.

“In order to get some idea of the amount of error which might be expected through the use of abdominal palpation to establish the plane in which the occipito-

frontal diameter lies, we conducted a series of shadowgraph experiments with a full-term infant skull, a screen, and a reflected light.

"It was found that the fetal skull could be rotated in either direction 36 degrees before the shadow of the occipitofrontal diameter was shortened a millimeter. Moving the skull forward, still maintaining its parallel position with the screen to a 13 cm. distance, reduced the shadow two millimeters in the occipitofrontal diameter, while moving the skull to 17 cm. distance increased this shadow two millimeters." We feel therefore, that the method is accurate within two to three millimeters and our results seem to support this contention.

At the time of my first communication on the subject of fetal maturity, in order to establish a working base, a statistical study was made of a relatively large number of children to determine the relationship of occipitofrontal diameter to fetal length and body weight. In a review of 446 newborn infants, 369 measured 45 cm. or over. Eighty-seven per cent of those cases which presented an occipitofrontal diameter of 11 cm. or more showed an accompanying crown heel distance of 50 to 55 cm.; 90 per cent of those cases presenting an occipitofrontal diameter of 10.5 or over showed a crown heel distance of 45 to 50 cm.; 73 per cent of those cases presenting an occipitofrontal diameter of 9.5 to 10.5 cm. showed a crown heel distance of 40 to 45 cm.; and 100 per cent of the cases showing an occipitofrontal diameter of 7.5 to 9.5 cm. showed a crown heel length of 35 to 40 cm. It would appear from these studies that in a given instance, an occipitofrontal diameter of over 10.5 cm. would be evidence of an accompanying crown heel length of 45 cm. or more.

In the relationship of the occipitofrontal diameter to the body weight 453 cases, all 3,000 gm. or under, were reviewed with the following results:

#### RELATION OF BODY WEIGHT TO OCCIPITOFRONTAL DIAMETER

Total cases reviewed: 453

Weight 2,500 to 3,000 gm.	327 cases, of which 264, or 80.9 per cent, had occip. frontal diameter 11 cm. or more.
Weight 2,000 to 2,500 gm.	81 cases, of which 69, or 85.2 per cent, had occip. frontal diameter 9 to 10 cm.
Weight 1,500 to 2,000 gm.	39 cases, of which 27, or 69.2 per cent, had occip. frontal diameter 9 to 10 cm.
Weight 1,200 to 1,500 gm.	6 cases, of which 4, or 66.7 per cent, had occip. frontal diameter 8 to 9 cm.

It would appear from this table that in the instances where the occipitofrontal diameter is over 10.5 cm. an accompanying body weight of 2,500 gm. or over may be expected.

Table I represents the findings in the last 25 cases in which we have used roentgen cephalometry as a means of determining fetal matur-

ity. The maternal indications for the termination of pregnancy have included tuberculosis, pyelitis, toxemia, pernicious anemia, disproportion, and heart disease.

TABLE I

CASE	OCCIP. FRONTAL DIAMETER IN UTERO	TYPE OF BIRTH	OCCIP. FRONTAL DIAMETER AT BIRTH	CROWN HEEL DISTANCE AT BIRTH	WEIGHT AT BIRTH	HISTORY NO.
	cm.		cm.		gm.	
1	11.5	Cesarean section	11.7	51.0	3545	S8010
2	10.5	Labor induction	11.0	48.0	2355	S8699
3	10.3	Labor induction	10.2	48.0	2545	S8855
4	11.5	Normal spontaneous	11.5	---	2920	S4914
5	11.5	Cesarean section	11.6	---	3400	60826
6	10.8	Normal spontaneous	11.0	48.0	3080	51121
7	13.0	Cesarean section	12.75	---	---	(p.p. Dr. C.)
8	12.75	Cesarean section	12.5	---	4022	(p.p. Dr. C.)
9	11.5	Cesarean section	12.0	50.0	2740	S9232
10	11.75	Normal spontaneous	12.0	50.5	3025	57839
11	10.5	Normal spontaneous (see text)	11.5	49.0	3360	A29086
12	11.3	Cesarean section	11.4	50.0	3085	A40414
13	10.4	Cesarean section	10.5	45.0	2055	A15343
14	10.4	Cesarean section	10.6	47.0	2550	54842
15	10.0	Labor induction	10.2	44.5	2240	A44959
16	11.25	Normal spontaneous	11.25	49.0	3045	-----
17	11.0	Normal spontaneous	11.5	51.3	3945	A29986
18	11.25	Normal spontaneous	11.75	51.0	4110	A18383
19	11.0	Normal spontaneous	11.25	48.0	2890	A29354
20	11.0	Normal spontaneous (excessive molding)	12.0	47.5	3070	4556
21	9.25	Labor induction	9.75	---	1800	44798
22	12.0	Normal spontaneous	12.0	51.0	3455	A16700
23	10.3	Normal spontaneous	10.5	47.5	2960	-----
24	11.25	Normal spontaneous	11.25	50.0	3125	A36803
25	11.25	Normal spontaneous	11.25	48.5	3145	64337

A survey of the above table offers interesting data for discussion. Those cases delivered by cesarean section, and therefore not subject to molding, show but little discrepancy between the intrauterine and postpartum measurements. In seven of the eight cases the difference was 2.5 mm. or less. There is no question in my mind, that molding which is incident to birth by the natural passages, often does affect the length of the occipitofrontal diameter. In most cases, however, this effect is not as great as usually supposed. When excessive molding has taken place as in Case 10, marked discrepancy may be expected.

I wish to call attention to Case 11 as it emphasizes another point to which I have referred. The cephalogram in this case was made when the patient had experienced four hours of active labor and the occiput was definitely in the right occipitoposterior position and deeply engaged. This condition is easily discernible in the film, and a marked discrepancy in the intrauterine and postpartum measurements was expected.

The last ten cases of this series are those taken in connection with a study of fetal head molding and the postpartum measurement was made by means of roentgenometry exactly one hour after the birth. This method was used in order to eliminate the thickness of the scalp and the results are very accurate. I am confident that the uniformly slight increase in the postpartum measurement of the occipitofrontal diameter in these cases is the result of molding incident to birth.

To summarize this series, excluding Case 20 and Case 11, we find that there was no difference in the antepartum and postpartum measurement in four cases; a difference of 1 mm. in 4 cases; a difference of 2.00-2.5 mm. in 10 cases; a difference of 5 mm. in 5 cases.

I am convinced that the best index to fetal age is that of fetal length or crown heel distance. Reed<sup>5</sup> has emphasized the fact that the fetus puts on weight in the uterus as easily and as variably as after birth, and that it appears that weight is a sign of present nutrition while length is an indication of past assimilation. Bossi<sup>6</sup> regards the weight of the fetus as of no importance in the diagnosis of postmaturity but places great reliance on the fetal length in association with the development of the bones. It appears, therefore, that in discussing fetal maturity, we should become more familiar with the fetal length relationship rather than the traditional fetal weight relationship. The proof of this is exemplified in Case 12 where the infant delivered by cesarean section had a crown heel distance of 45 cm. and a body weight of only 2,045 gm.

To recapitulate: (1) The estimation of fetal maturity in utero by means of determining the length of the fetal occipitofrontal diameter is a most useful clinical procedure. (2) The grid method which in this clinic and elsewhere has given satisfactory results has an advantage in that it is unusually rapid and simple to carry out. (3) The best estimate of fetal maturity is found in its relationship to fetal length or crown heel distance. Obstetricians should, therefore, familiarize themselves with this relationship.

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## TUBERCULOSIS AND PREGNANCY

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FOR twenty centuries, since the time of Hippocrates, it has been claimed that tuberculosis often improves with pregnancy. There were periods when marriage with subsequent pregnancy was actually recommended for tuberculous girls. Such views were held by Sydenham, Montgomery, Clark, Warren and many others. As recently as 1918 Sabourin recommended marriage for tuberculous girls because of a resultant "degree of immunity."

Ingraham<sup>1</sup> believes any actual improvement that takes place may be due to enforced rest necessitated by pregnancy. He feels that such improvement is likely to be only temporary and that "after the fifth or sixth month, rapid advancement of the disease usually occurs." In 1932 Fishberg<sup>2</sup> wrote, "it appears that many women with active tuberculous disease feel much better, the symptoms of the disease abating to some extent during pregnancy. Perhaps an explanation may be found in the circulatory changes occurring during pregnancy. It is well known that during that period the mucous membranes of the respiratory tract are congested, and this may retard the progress of the tuberculous process for the time being, as is seen to be the result of pulmonary congestion in cases of mitral stenosis."

On the other hand Ferguson<sup>3</sup> states that "pregnancy at any stage, and especially when allowed to go to full term, has no ultimate or real beneficial effect on tuberculous disease." Some writers feel it is dangerous, at any stage of the disease, for a tuberculous patient to become pregnant, others going so far as to recommend emptying of the uterus in all such cases. Several authorities are of the opinion that pregnancy should be avoided by the tuberculous woman until a "cure" has been established for two or three years. Many others hold that pregnancy in the tuberculous patient has a marked deleterious effect on the disease, their opinions varying only in the degree of danger.

Hanau feels that the disease may be aggravated by aspiration of tubercle germs from upper to lower parts of the lungs following descent of the diaphragm after labor. Others have thought that anemia following loss of blood in normal labor has resulted in further disease activity, and quite a few writers blame the reactivity on the shock and strain that might occur during delivery of the child.

Forssner<sup>4</sup> in an extensive study contradicts a harmful effect on the disease by pregnancy, at least when the disease is early. Adair and Whitacre<sup>5</sup> give detailed figures pointing to the harmful effect, when the disease is in the second and third stages, being so slight that it may be due simply to the result of chance. They feel that harmful influence in advanced cases of tuberculosis cannot be denied. Very interesting is the conclusion of Jennings and Mariette<sup>6</sup> in studying 470 cases, who say "the evidence is striking that the phenomena are independent of one another." It is known that a tuberculous woman very rarely dies with a fetus in utero.

It is apparent from the mass of contradictory material available that a great deal more work will be required to unfathom these com-

plexities. This paper is intended merely to suggest a possible explanation for a few of the observations on the subject. The case given here for obvious reasons is not conclusive in any way, but it is hoped will result in discussion of the points involved.

Previously the recognized treatment for pulmonary tuberculosis was purely medical and consisted chiefly of bed rest, fresh air and sunlight, and proper food. Now, however, in modern institutions approximately 80 per cent of the patients receive some form of collapse therapy, permitting physiologic rest of the diseased area. The surgical procedures used are chiefly phrenic nerve operation, pneumothorax and thoracoplasty or a combination of these.

Phrenic nerve operation results in the paralysis of the diaphragm on the affected side, followed by as much as one-fourth to one-third limitation of lung expansion. There are two forms of this operation

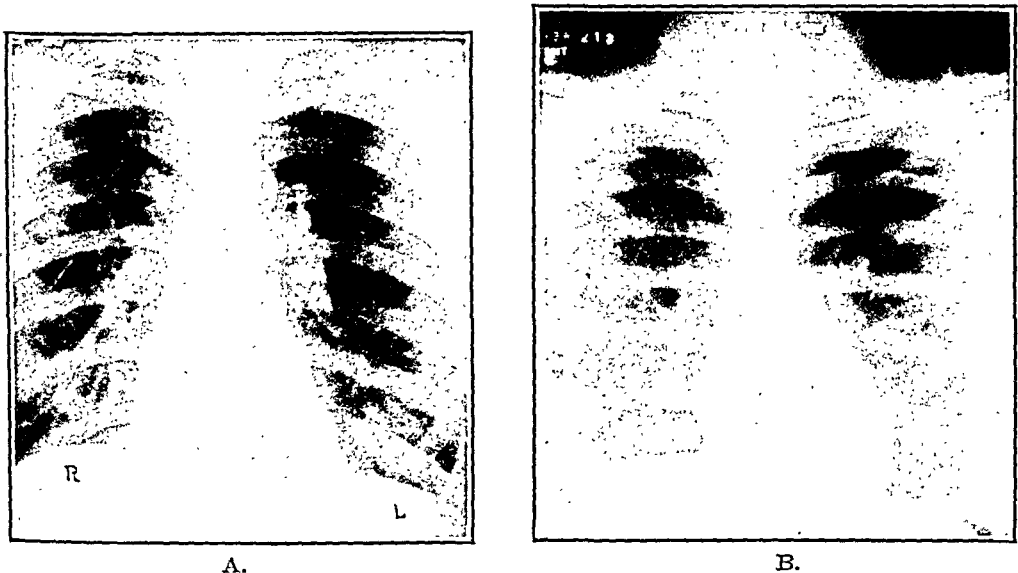


Fig. 1.—A, Showing tuberculosis in the middle of the right lung, with a cavity. Note the level of the leaves of the diaphragm, (R) right (L) left. B, The same patient approximately one month later, showing closure of the cavity, following a phrenic nerve operation. Note the elevation of the paralyzed diaphragm (R) on the diseased side.

(a) crushing of the phrenic nerve, giving a temporary paralysis and (b) phrenicectomy, resulting in permanent paralysis. Phrenic nerve operation is first choice in early disease in a basal lesion or when there is a small cavity. It is also used in selected more advanced cases where pneumothorax is impossible because of pleural adhesions, the chief drawback to success in suitable pneumothorax patients. A phrenicectomy is advisable, too, when allowing a lung to expand after pneumothorax.

Fig. 1, A shows pulmonary tuberculosis in the middle of the right lung, with a cavity and B the position of the diaphragm following a phrenic nerve operation with resultant closing of the cavity. This case is shown for comparative purposes.



Fig. 2, A shows the x-ray of a young woman, age twenty-two, two months pregnant. There is an area of tuberculous infiltration in the right second interspace; B shows the same patient just one week before the normal termination of pregnancy, with the tuberculous lesion healed. It is my contention that this healing could easily be the result of what might be called a physiologic bilateral elevation of the diaphragm, following the pushing upward of the abdominal contents in advancing pregnancy, simulating a phrenic crushing. An x-ray photograph of this patient six months after delivery showed no return of the disease.

Thus Fig. 2 may explain the reason for what has frequently been previously observed; namely, that some tuberculous women show improvement of the disease during pregnancy. It could also explain



A.



B.

Fig. 2.—A, X-ray of a young woman, aged twenty-two, two months pregnant, showing early pulmonary tuberculosis at second right interspace. B, The same patient one week before normal labor, showing the tuberculous lesion healed. The elevation of the diaphragm here is due to pressure upward of the increased abdominal contents.

another oft discussed point, that is, the danger in the puerperium in these patients. The degree of diaphragm elevation, and the early lesion involved in Fig. 2, resulted in complete healing before the leaves of the diaphragm dropped to the normal position following delivery of the child. Were the disease still unhealed, however, one can appreciate that the sudden return of full lung expansion may result in further activity of the lesion, which, if left untreated, might go on to fatal termination.

#### CONCLUSIONS

Advancing pregnancy results in elevation of the diaphragm similar to that following a phrenic nerve crushing.

Though it is recognized that a single case proves very little, and appreciating that it cannot be accepted as conclusive even in the patient involved, nevertheless it is presented to stimulate discussion on the points mentioned.

If the theory is correct it definitely explains an observation made over centuries but attributed to other reasons, that is, the frequent improvement especially of early cases during pregnancy.

The rapid increase of the disease in tuberculous women immediately following labor may be explained by the sudden removal of the beneficial effect due to elevation of the diaphragm.

It is suggested that pregnancy in tuberculous women is a matter for consultation of the obstetrician with the chest specialist as to the proper procedure during and after the completion of the pregnancy. Proper collapse therapy just previous to delivery will undoubtedly improve the outlook in what might otherwise become a more serious condition.

Since it is known that up to 1 per cent of apparently healthy young adults may have active tuberculosis,<sup>7</sup> it is strongly advisable that all pregnant women, particularly primiparae, have an x-ray of their chest at least in the latter part of pregnancy, *irrespective of the presence or absence of symptoms or abnormal physical signs*. In this way previously unsuspected tuberculosis may be found and proper collapse treatment instigated before severe damage results.

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8921 HAMILTON AVENUE

Ryerson, and Sanes: The Age of Pregnancy, Arch. Path. 17: 648, 1934.

In a study of placental tissue based upon the maturation of red blood cells in the fetus, with their development from nucleated to nonnucleated forms, the authors state that they are able to determine the age of a pregnancy. A differential enumeration of these elements in the chorionic capillaries is made and the results may be expressed in quantitative terms. The procedure consists in the examination of material obtained from paraffin sections and stained with hematoxylin and eosin. One hundred consecutive specimens of placental tissue were examined. This material was obtained following full-term delivery, curettage, abortion, or operation for ectopic pregnancy. Appropriate clinical histories accompanied all specimens. The proportions of nucleated to nonnucleated red blood cells were calculated.

Of seventy placental fragments suitable for study, it was found that replacement of nucleated by nonnucleated forms took place rapidly and almost completely during the second and third months. Therefore, if all the chorionic corpuscles are nucleated, the pregnancy is probably not older than two months. If more than 1 per cent are nucleated, the age is less than three months. If fewer than 1 per cent of the red cells are immature, pregnancy has passed beyond three months. This method, the authors claim, may be of medicolegal value.

W. B. SERBIN.

## TUBAL ENDOMETRIOSIS SIMULATING ECTOPIC PREGNANCY\*

J. IRVING KUSHNER, M.A., M.D., NEW YORK, N. Y.

*(From the Department of Pathology and Medical Research, The Bronx Hospital)*

WHILE the frequency of endometriosis in tubal pregnancy is admitted, yet the literature reports only four such instances. Seitz<sup>1</sup> reports a case of tubal menstruation and formation of an acute hematosalpinx mistaken for a ruptured tubal pregnancy. Lee<sup>2</sup> reports a case of a ruptured endometrial cyst simulating intraperitoneal rupture of an ectopic pregnancy; and Sampson<sup>3</sup> cites two patients with postsalpingectomy endometriosis operated upon for tubal pregnancy. In both cases an endometriosis of both uterine cornu without evidence of decidual reaction were found.



Fig. 1.—Wall of tube. Hyperplasia of wall. Uterine-like endometrial stroma, with some congestion.

The paucity of the literature on this condition led to the report of the following case:

B. G. (No. 39992), white female, aged thirty-five, admitted to the hospital because of pelvic pain and vaginal bleeding. Menses had begun at age of twelve, were of twenty-eight-day type, regular, with a four-day flow. Patient had missed her last period and almost immediately began to experience vague pelvic pain, weakness, and five days later slight vaginal bleeding.

On examination, because of tenderness in left lower quadrant, with slight enlargement of the uterus and a fixed tender mass in the left culdesac, a diagnosis of ectopic gestation was made and immediate laparotomy performed.

At operation the entire left adnexal region was found to be the seat of a mass intimately matted together about the size of an orange. There was no free blood found in the pelvic cavity. A left salpingo-oophorectomy was performed.

\*Read at a meeting of the North Bronx Medical Society, November 1, 1934.

The complete pathologic report is as follows: Specimen consisted of an irregular mass 6 by 5 cm., composed of a tube and ovary intimately connected. The ovary was whitish in color, fibrotic, and contained a large irregular corpus luteum cyst. Tube was distorted, apparently the seat of a large rupture, and lumen contained some blood clots. Microscopic section of tube showed the lining hypertrophic and congested. It had the appearance of uterine endometrial stroma. There was no evidence of decidual reaction. Diagnosis: "Hyperplastic endometriosis, tubal."

I wish to express my appreciation to Dr. Joseph Felsen, Director of Laboratory and Medical Research at The Bronx Hospital for his helpful suggestions in the preparation of this report.

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169TH STREET AT FULTON AVENUE

## A CASE OF TUBERCULOUS INFECTION OF THE BARTHOLINIAN GLAND

ANTHONY BASSLER, M.D., NEW YORK, N. Y.

IN A SEARCH of the literature I could find no instance of tuberculous infection of the Bartholinian gland, and therefore believe the following case worthy of record.

The patient came under my observation in July, 1928. She was then twenty-one years of age, single, born in the United States. Other than an appendectomy done seven years before to relieve intermittent abdominal pains, there was nothing important in the past history of moment. Following the removal of the appendix the abdominal pains continued, after which several different diagnoses were made to account for them. At the time of my first observation she reported to have lost in vitality and strength, becoming progressively worse each year although her appetite remained good. She stated that she was eleven pounds below her top weight. The abdomen presented a large, protuberant, diffuse mass occupying all of the area below the umbilicus. Temperature 101° F., pulse 90, white cell count 12,100, with 79 per cent polymorphonuclears. The patient being in marked distress, the abdomen was opened three days later and the appearance was that of an extensive tuberculous peritonitis. A thorough aeration was done and the abdomen closed. Moderate local improvement took place and four months afterward the condition had returned as before with three discharging sinuses of the tuberculous type in the scar. Several intraperitoneal injections of oxygen were given without any benefit, the entire abdominal condition finally clearing up with the intensive use of quartz lamp treatments, the sinuses also closing, and the woman remaining in good health ever since.

In April, 1934, there began a painless and noninflammatory swelling in the right vulva, no constitutional symptoms being connected with it. The only complaint was interference on sitting. The vulva in the locality of the Bartholinian gland on that side presented a cold, edematous swelling, extending from the perineum forward to about half of the vulva and up to the introitus. This was incised and a glairy, colorless, jellylike fluid discharged. Several days later the wound had healed and most of the swelling had subsided. Within a few days, the swelling returned about

as before and a second incision was done, the same sort of material obtained as before, and the wound packed. Quick healing of the wound permitted packing for only a few days. A return of the condition took place as before. Complete excision of the gland was then done, following which complete recovery took place.

The examination of the tissue removed was that of typical Bartholinian gland structure with considerable round cell infiltration throughout areas of the gland tissue. One minute tubercle was present, the central part of which contained a giant-cell and considerable protoplasm with a great number of nuclei arranged around its periphery. The tissue was not stained for tubercle bacilli but the pathology was definitely that of a tuberculous infection, which in view of the tuberculous character of the case and the clinical character of the local condition, warrants belief that a tuberculous infection of the Bartholinian gland can take place. Evidently the condition is very rare, and from the experience with this case, it would seem that when the condition exists, excision of the gland is essential for a cure of the condition.

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## RECURRENT HYDROCEPHALUS

H. R. LELAND, M.D., MINNEAPOLIS, MINN.

THE occurrence of successive hydrocephalic children in the same woman is a very rare event and the paucity of such cases warrants this case report.

The patient, Mrs. A. G., aged twenty-two, married three years. Her mother had three children, all normal. The grandmother had 10 children, all normal. A sister had one child which was normal. On her husband's side, his mother had 4 children, all normal and his grandmother had 2 children, both normal.

The menses had always been irregular, four- or five-day flow, no pain. Her first pregnancy resulted in a breech presentation with perforation of a hydrocephalic head and delivery. There was a normal puerperium. The second pregnancy occurred one year later. All findings, including the laboratory, were negative except that the abdomen, on palpation, revealed an excessively large head over the pelvic brim. This was verified by x-ray examination to be hydrocephalic. She delivered a second hydrocephalic child which lived two months.

# MUCUS TRAP FOR TRACHEAL INSUFFLATION IN NEWBORN INFANTS MODIFIED FOR THE ADMINISTRATION OF OXYGEN AND CARBON DIOXIDE

MELVYN BERLIND, M.D., BROOKLYN, N. Y.

A MODIFICATION of the mucus trap for tracheal insufflation in the treatment of asphyxiation in the newborn is here presented. The change consists in the addition of an extra inlet for the purpose of administering oxygen and carbon dioxide during the insufflation. The percentages used are 95 per cent oxygen and 5 per cent carbon dioxide, although straight oxygen might also be used.

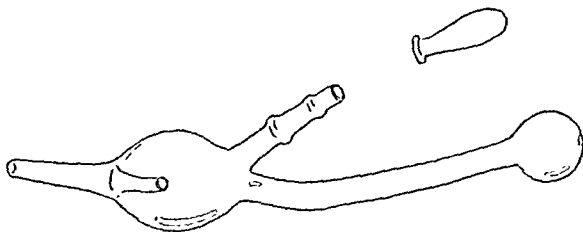


Fig. 1.

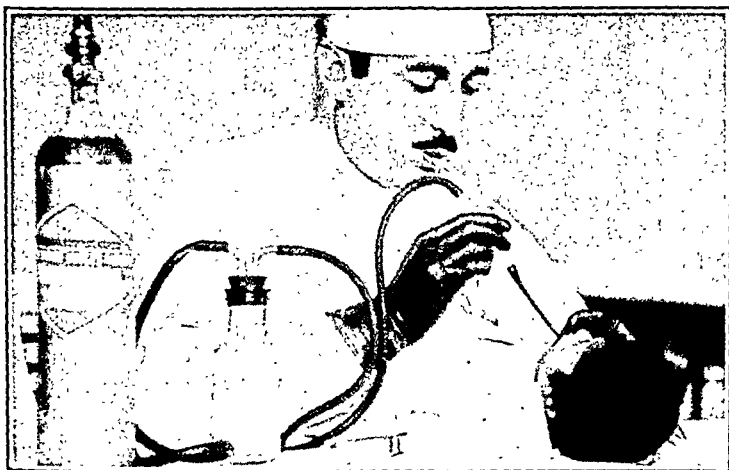


Fig. 2.

The advantages of this mucus trap appear obvious. It allows a high percentage of oxygen to come in direct contact with the pulmonary alveoli and thus very rapidly to decrease the primary cyanosis. The pressure under which the oxygen and carbon dioxide mixture is given can be gauged by the bubbling in the water bottle; a safe speed is approximately 100 bubbles per minute. Should the mucus trap be used without the oxygen-carbon dioxide tank, a nonperforated rubber nipple could be placed over the extra inlet. The catheters used are Nos. 10 and 14 French for premature and full-term infants, respectively.

My experience has been that the asphyxiated babies breathe earlier, with greater ease, and there is a marked and lasting improvement in their color with the addition of the oxygen and carbon dioxide. On occasion, I believe, it may be the factor in aiding to turn the scales in a seriously asphyxiated infant.

The mucus trap can be obtained from Eimer and Amend, New York.

125 EASTERN PARKWAY

## ROTRACTOR OBSTETRIC FORCEPS

M. NORMAN MOSS, M.D., ST. PAUL, MINN.

IN GOING over the literature on old, new, and modified obstetric forceps, one wonders whether it is possible to devise a new forceps or improve on an old one, without infringing on one which has already been described before.

In the May, 1928, issue of this Journal I described a cephalic rotating forceps. The instrument was purely a rotator and recommended in transverse arrest of the head and posterior positions, to help bring the head into a more favorable diameter for final extraction with the regular Simpson forceps. It was the usefulness of this instrument, which prompted me to seek a forceps capable of combining the function of rotation with that of traction. The instrument described herein, is the end-result of that effort.

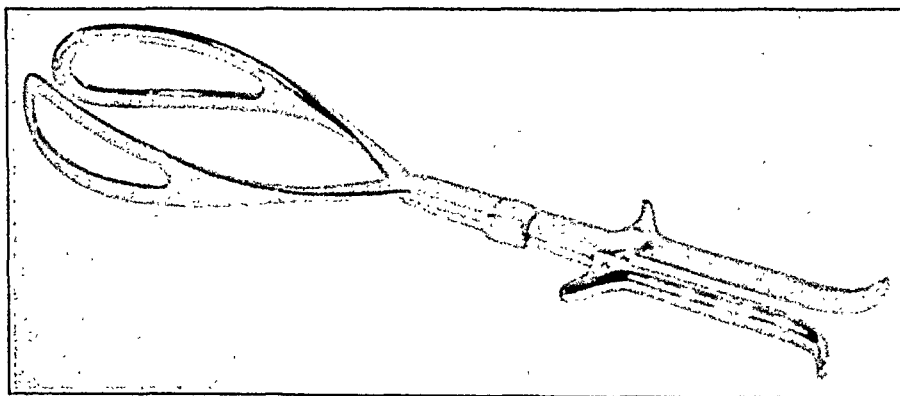


Fig. 1.

As one may observe from Fig. 1, the cephalic curve remains the same, while the pelvic curve is completely eliminated. The anterior and posterior edges of the blades are identical in every respect, thus permitting either blade to be inserted first and rotation made in either direction, without danger of gouging the ends of the forceps into the soft parts of the pelvis. The handles are identical to those of the Kielland forceps, being lighter in construction and much longer than those of the Simpson forceps. This feature is desirable, because it makes the instrument far more efficient in higher applications, as is usually the case in abnormal positions of the head.

Before making an application of the forceps, one must be positive of the exact position of the head, the membranes must be ruptured and the cervix completely, or nearly so, dilated. The hand is inserted and brought to the parietal side of the head and the blade is guided into position at this point. With the same hand still in the same position, the other blade is now inserted in the same manner and by means of the fingers guided around to the opposite side of the head. The blades

are now locked and gentle traction as well as slow rotation is made, both at the same time (corkscrew maneuver). When the occiput is brought into the anterior position and down to the pelvic floor, traction is continued in a straightforward direction instead of upward, as one usually does with the regular forceps. This latter change in direction of pull is necessary because of the fact that the retractor has no pelvic curve.

During the past year, the retractor is the only forceps I have used for instrumental delivery of any type. I have found it just as efficient in cases where the Simpson forceps is usually employed, but of utmost value in posterior positions and in transverse arrest of the head.

NEW LOWRY MEDICAL ARTS BUILDING

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## RECURRENT TUBAL GRAVIDITY ON THE SAME SIDE

JOSEPH DEUTSCH, M.D., AND JACOB CLAHR, M.D., NEW YORK, N. Y.  
(From the Departments of Surgery and Pathology of the Morrisania City Hospital)

**R**ECURRENT tubal gravidity on the same side is a very rare occurrence. This case is the only one encountered at the Morrisania City Hospital since July, 1929, during which time 88 patients with ectopic gestations were admitted. A complete study of the literature was made by Hasselblatt<sup>1</sup> in 1926, from which he was able to collect 19 cases, plus the addition of two new cases of his own. In his article he gives a summary of each of the 21 cases, and since they are for the most part similar to ours, it will be needless to quote his presentations. We have further reviewed the literature and found 8 additional cases,<sup>2 3</sup> of which were interstitial tubal pregnancies and 5 in other portions of the tube. In this entire group of cases we also found two patients who had a triple occurrence of tubal pregnancy. The frequency of interstitial pregnancy (3 out of 8 cases) is quite common. It is important to note the associated absence of vaginal bleeding, which though not constant, is characteristic of the interstitial type. This is mentioned and emphasized by McIntyre,<sup>3</sup> Robinson,<sup>4</sup> and Vineberg.<sup>5</sup>

Our patient, a white woman, aged twenty-seven, married, was admitted to the Morrisania City Hospital Sept. 5, 1933, with the chief complaint of "pain in the lower abdomen and the right shoulder." Four days before admission, the patient noticed a lump in the lower right abdomen, which was tender to the touch, but not painfully so. On September 5, while being examined by her physician, vaginally, she complained of intense cramplike pains across the lower abdomen and fainted. Subsequently this pain radiated to the right shoulder. She was sent into the hospital, from the doctor's office, in shock.

This patient has been pregnant three times, twice delivered at term, and once operated upon for an ectopic gestation. Menses started at the age of fifteen years, occurred every three to five weeks and lasted seven days. Her last regular period was July 22, 1933. For two days prior to admission she had been spotting.

The patient was operated upon Dec. 18, 1931, for an ectopic pregnancy of the right tube. The right tube was removed at that time apparently leaving behind the interstitial portion.

Examination on admission revealed a pallid woman in shock with a pulse almost imperceptible. Her lower abdomen was tender and distinctly resistant, more emphatically on the right side. Rebound tenderness was marked. Vaginal examination revealed a mass in the lower right quadrant, filling the right fornix. The cervix was extremely tender on manipulation. There was no mass palpable in the culdesac.



The patient was treated for shock. It was noted that lowering the head of the table caused an exacerbation of the pain in the right shoulder. Fowler's position gave her more relief. A transfusion of 400 c.c. of whole blood was given before operation.

The blood count before operation was 23,000 white blood cells with 85 per cent polymorphonuclears and 12 per cent lymphocytes; 3,900,000 red blood cells and 85 per cent hemoglobin. The urine was negative.

The patient was operated upon soon after admission to the hospital under ether anesthesia. A median suprapubic incision was made, removing the old scar. The peritoneal cavity was found to be filled with blood clots. A large amount of this was removed. The uterus was brought through the wound and found to be slightly enlarged. A ruptured ectopic gestation was found located in the right cornua of the uterus. The tube itself was absent. The right ovary was adherent to the interstitial portion of the right tube. The left tube was normal and the corresponding ovary contained a corpus luteum vera. The cornua of the uterus containing the ectopic gestation including the ovary was removed by excision. The area was then closed by continuous suture and peritonealized. The abdominal wall was closed in layers in the usual fashion.

The patient made an uneventful recovery and was discharged on the tenth day postoperative.

Examination of the removed tissue disclosed an ovary closely adherent to the excised cornua of the uterus, which measured 2.5 cm. in circumference. It was smooth on its surface and contained many small cysts varying in size from a pin-head to 3 mm. in diameter. The mesial portion of the ovary was hemorrhagic and formed part of the wall of the ectopic gestation. The excised cornual portion of the uterus was also round and after fixation measured 3 cm. in diameter. It presented a ragged opening on its anterior wall which measured 1.5 cm. in diameter. Through this opening a very early placenta protruded containing an umbilical cord. On cut section the lumen of the tube was found to be dilated to 2 cm. in diameter with its wall measuring  $\frac{1}{2}$  cm. in thickness and its inner surface irregular and hemorrhagic. The uterine end of the interstitial portion of the tube did not contain its lumen.

Microscopic examination of the ovary disclosed several normal graafian follicles, engorged vessels, and enlarged stromal cells resembling decidual cells. Section through the placenta presented normal villi covered by a double layer of trophoblastic cells. The tube was made up of swollen muscle cells invaded by chorionic villi, chorionic wandering cells, and masses of trophoblastic tissue.

In our case the ovum came from the opposite side. It may have passed normally down the left fallopian tube, become fertilized, and entered the uterine orifice of the right tubal stump; this is extremely improbable. It is far more likely that the ovum, originating from the left ovary, crossed the peritoneal cavity and found its way into the tubal stump, which had regained its patency.

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# SUPERNUMERARY MAMMARY GLAND TISSUE ON LABIA MINORA

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THOUGH accessory breast tissue has been known to occur on almost every part of the body surface, the appearance of bilateral mammary gland anlage on the labia minora seems out of the ordinary.

Mrs. G. S. (Hospital Number D-1250), aged twenty-four, gravida 5, was admitted to the Obstetrical Service of the University Hospital on May 30, 1929, about two weeks from the expected date of confinement. The pregnancy had been completely normal except for a mild hypochromic anemia. At routine antepartum examination, a soft, spherical, semicystic mass about the size of a plum stone was noted in the right labium minus adjacent to the clitoris (Fig. 1). A similar lump about half as large was present in the left labium. There was no inflammatory reaction. A

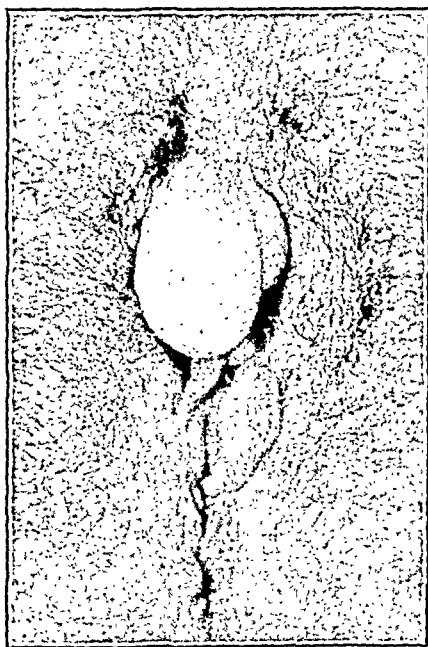


Fig. 1.—Photograph taken seventeen days postpartum. At this time the nature of these masses was not known. They were removed the following day.

provisional diagnosis of lipoma of the vulva was made. The patient had a spontaneous labor on June 10, 1929, giving birth to a normal male child. No further attention was given to the vulval masses until June 27, 1929, when the mass on the right measured 2 cm. and that on the left 1 cm. in diameter. The following day they were removed under general anesthesia.

*Pathologist's Report.*—"The tissue for the most part is glandular, which is separated into lobules by fibrous connective tissue. Two of the sections are covered on one side by a layer of stratified squamous epithelium in which an occasional hair follicle is seen. The acini vary much in size. Many are dilated, forming cystic

cavities in which a light staining material is found. The gland cells are cuboidal and are low cuboidal in the larger alveoli. The nuclei are large, ovoid, and vesicular. The cytoplasm contains droplets of fatty material. An occasional alveolus is found in which a second layer of cells is found forming a basement membrane. The nuclei of these cells are spindle shaped and resemble involuntary muscle. Diagnosis: Breast tissue, supernumerary." (Fig. 2.)

The report aroused so much interest that additional information was sought concerning the history of these accessory breasts. The patient stated that they were

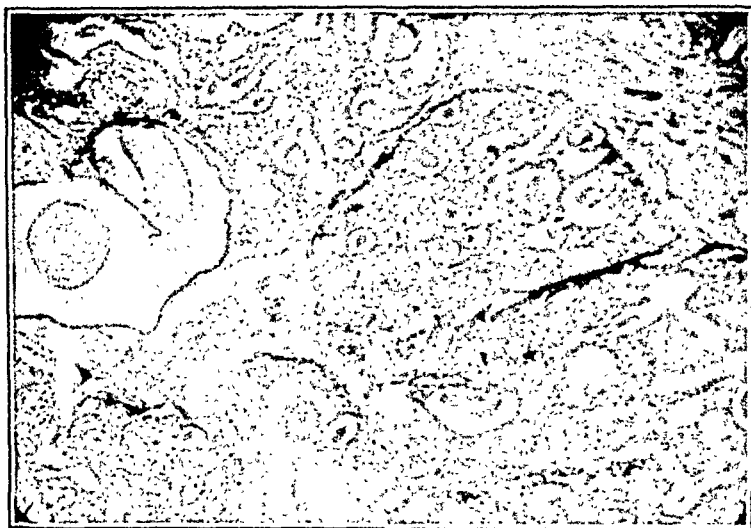


Fig. 2.—Photomicrograph of sections of the right labial tumor shown in Fig. 1. Note the secretion in the dilated, cystic acini.

not noted during the first three pregnancies, but that during the second month of the fourth pregnancy her family physician noticed a swelling near the clitoris, and in the fourth month the patient noticed it herself. The lump gradually became larger until delivery, following which it was tense and painful for about four days and then subsided to become impalpable. During the present pregnancy it followed a similar course.

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Petit-Dutaillis, P.: The Value of Weight in the Detection of the Arrest, Persistence or Recurrence of an Epithelioma of the Cervix After Treatment, *Gynécologie* 32: 193, 1933.

It is generally accepted that recurrences of carcinoma more than five years after treatment are extremely rare. But it is a mental hardship for a woman or her family to wait five years to be sure of a cure. Most individuals would like to know the prognosis long before the five-year period has elapsed. Petit-Dutaillis is of the opinion that in the weight of the patient we have a reliable index of the success or lack of success in therapy. A weight chart must be kept, beginning at the time the treatment is begun. The weight should be taken regularly once a month under approximately the same conditions. If a woman gains in weight after treatment, the cancer is not progressing or there is not a recurrence. The more the gain in weight and the more rapidly this takes place, the more favorable the prognosis.

## PROLONGED RETENTION OF FETUS FROM AN EXTRAUTERINE PREGNANCY

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(*Departments of Obstetrics and Pathology, St. Luke's Hospital*)

MANY amazing instances are on record of prolonged retention of an extrauterine pregnancy and there are records of successive pregnancies during such retention. The ultimate fate of the retained fetuses is likewise a matter of considerable interest. After a certain period of gestation, the fetus cannot be absorbed after it dies, and hence with the entry of microorganisms may undergo secondary infection, suppuration, and even partial autolysis. The infected parts may necrose into the bowel or even through the abdominal wall and be thus expelled if the patient does not succumb to the infection. Sometimes these fetuses become mummified or calcified and at times may even undergo adipocere degeneration.

CASE 1.—Mrs. W., aged sixty-nine, entered the hospital because of pain and enlargement of the abdomen of about three months' duration. The pain started in the lower abdomen and gradually became more or less generalized. She had had trouble with "bloating" for about nine months prior to her hospital admission. The history was otherwise negative except for the statement that thirty-five years previously she had a miscarriage and was never again pregnant.

Examination showed an enlarged, dense, tympanitic abdomen with a definite fluid wave. Roentgenographic examination revealed inadequate filling of the cecum, many diverticuli in the descending colon, and a calcified mass about the size of a grapefruit in the left lower quadrant. This calcified mass was removed and at this time considerable fluid was found in the abdomen. Although at operation a possible carcinoma of the cecum was suspected, none was found. The patient continued with her former symptoms and had considerable vomiting. Another exploratory laparotomy was performed and about two-thirds of the stomach was found to be involved by a large carcinoma, which extended into the head of the pancreas. Omental metastases were found to be partially obstructing the middle portion of the ascending colon. The patient subsequently left the hospital and no later history was obtained.

*Pathology.*—The specimen was a heavy semicalcified, more or less spherical, tumor mass, rusty brown in color and covered with shaggy adhesions. It measured 11 by 9 by 9 cm. and on cross-section it was extremely difficult to cut. Masses of hair, skull and fetal parts presented themselves and intact arms and legs were readily discernible. This tumor when first examined was thought to be a calcified dermoid cyst and was so diagnosed. When the second case was observed, however, the similarity of the two specimens was so striking that this tumor was re-examined and roentgenograms revealed the bony skeleton and partially intact fetal parts.

CASE 2. Mrs. M., twenty-four years of age, was seen by one of us (T.H.A.) when admitted to the Kansas City General Hospital complaining of pain in the right side. She was apparently threatening to abort. She gave a history of having had gonorrhea the past four years. Her last normal period was six months previously. At the next period she flowed only about fifteen minutes and from this time on she had a tendency to flow for about ten or fifteen minutes every time she did any heavy lifting. Four months after her last period she had a large flow with

sharp pains in the right side. She had fainted several times and had aching in the right side, which symptom, however, had been present more or less all of her life. For the past four months she had had some flowing after any type of moderately strenuous exercise. For the first three months of her supposed pregnancy, she had nausea and vomiting; and at the fourth month felt movement, which continued until one week prior to entry in the hospital.

Examination at this time revealed a tumor mass rising two fingerbreadths above the umbilicus and "a placental souffle was heard over the pubis" but the fetal heart was not heard. The impression at this time was that of a six months' pregnancy with a possible dead fetus. A roentgenogram taken at this time to rule out abdominal pregnancy was recorded as "skeletal structure of fetus with head on the right side. The outline of the fetus is visible along the lateral margin. This is an intrauterine pregnancy" (Fig. 1). Vaginal bleeding ceased about the third day



Fig. 1.—Case 2. Roentgenogram erroneously diagnosed as "intrauterine pregnancy."

but pain at intervals continued in the right lower quadrant. The patient was then dismissed from the hospital on the ninth day and instructed to report to the Out-Patient Department; this she failed to do.

At the expected time the patient did not go into labor and the abdomen seemed to decrease in size. Her periods became normal every twenty-eight days and she consulted a physician who told her she was not pregnant but that she had a "fibroid tumor." She, therefore, returned to one of us (T. H. A.) six months after her first admission, or one year after she missed her first period. At this time, a pelvic tumor was found which was about the size of a grapefruit. It was hard and nodular in character and it was thought to be either a fibroid or perhaps a calcified intrauterine fetus. Operation was advised and the patient entered St. Luke's Hospital for operation three months later. A large mass was found in the right pelvic cavity which was enclosed in a membranous capsule. This mass and the appendix were removed and the patient had an uneventful convalescence.

*Pathology.*—The mass was covered with a grayish membrane and the entire specimen weighed 546 gm. The mass of sac and fetus was irregularly rounded and seminodular in shape and measured 14 by 10 by 7.5 cm. Fetal parts were easily palpable through the sac walls. On opening, no fluid was present in the sac. The fetus was mummified and dehydrated but all parts were easily identified.

Two cases of long retained extrauterine pregnancy are here recorded. One was possibly of thirty-five years' duration and was discovered in the roentgenogram as a pelvic tumor and removed during an exploratory operation for cancer of the stomach. On gross examination, it was considered to be a calcified dermoid but later dissection and roentgenograms revealed well-formed, skeletal parts in spite of the long retention. The second case was of fifteen months' duration, had been erroneously diagnosed as intrauterine pregnancy both clinically and from roentgenographic examination, but when the expected delivery failed to transpire a retained pregnancy was suspected which, on subsequent operation, proved to be extrauterine.

## PLACENTA PREVIA COMPLICATING TWIN PREGNANCY

M. W. HAWES, B.S., M.D., FULTON, KY.

IN THE August, 1934, issue of this JOURNAL, Gallagher-Heaton reported a case of twin pregnancy complicated by placenta previa. Seeing the following case a few days after receiving the JOURNAL stimulated my interest in this complication. In a rather hasty survey of the literature and after searching through three textbooks on obstetrics, I was unable to find any mention of a special way to handle these cases. I wish to add the following case of single ovum twins complicated by placenta previa.

Mrs. D. W., white, wife of a farmer, aged thirty-one, was admitted to the hospital Oct. 11, 1934, at 12:30 P.M. The patient was a para vi, having had four normal pregnancies and one five months' abortion; one and a half year previous to this pregnancy the patient had always enjoyed good health, except for childhood diseases. There was no history of twin pregnancies in either family of the wife or husband. The patient's menses began at the age of eleven, were regular, 28-day type and painless.

I saw the patient first in my office, July 6, 1934. At this time her blood pressure was 115/80 and urine negative; last menses occurred March 18, 1934. Estimated date of delivery being Dec. 25, 1934. In my neighborhood we have some difficulty in seeing our patients regularly; although this patient was urged to report monthly, I did not see her again until about 11:00 A.M., Oct. 11, 1934. At this time I received a hurry call to the patient's home. She gave a history of painless bleeding for about ten days, but because of her previous miscarriage thought very little about it. About half an hour before my arrival there had been a painless gush of blood. When I arrived, the patient was pulseless, very pale, and blood was flowing freely from the vagina. Being sure I was dealing with a placenta previa and seeing the patient was in extremis, I immediately packed the vagina, under as clean conditions as possible. The pulse could not be felt and the blood pressure reading could not be obtained. The pack controlled the bleeding and the patient was sent to the hospital at once.

On arrival at the hospital, the packing was removed and the patient examined. The diagnosis of partial placenta previa was confirmed, the placenta being on

the left side posteriorly, and only a small part extended over the cervix. The cervix was half effaced and dilated so that two fingers could be inserted. As the examination excited more bleeding and the patient was already in extremis, a No. 6 Voorhees' bag was hastily inserted and the vagina packed tightly. Patient was returned to bed at about 1:00 P.M. Blood pressure was still zero and no pulse could be felt. Intravenous saline with 5 per cent glucose was started and the patient was given 2,500 c.c. by 4:00 P.M. Donors for a transfusion were searched for but none would match.

At 4:00 P.M. the blood pressure had come up to about 50 and a small pulse could be felt at the wrist; red blood cells numbered 1,750,000 and 35 per cent hemoglobin. Patient had no pains after her return to bed, but due to the questionable conditions under which the first pack was inserted, and fear of infection, it was thought advisable to deliver her as soon as possible; hence she was returned to the operating room at 4:15 P.M.

On removal of the pack and bag, it was found that the cervix would accommodate four fingers with some little difficulty. The membranes were unruptured, and the baby was presenting by vertex. When the packing was removed bleeding recurred, so under a light ether anesthetic, we started to do a version and slow extraction. The membranes were ruptured and the posterior foot brought down. The version was easily completed, and we were greatly surprised when no resistance was offered to the birth of the baby, which was completed immediately. The baby weighed 2½ pounds, and made no attempt to breathe. Up to this time there was no suspicion of a twin pregnancy, but after the delivery of the first small baby, my suspicions were aroused. On palpating the uterus, which was still well above the umbilicus, another baby could be distinctly felt. The hand was reinserted into the uterus, the second membrane ruptured, and the second baby, weighing 2¾ pounds, was delivered easily by version and extraction. This baby also made no attempt to breathe. During these manipulations a small amount of bleeding had occurred and the patient had again become pulseless, so immediately following delivery of the second baby, the hand was reinserted and the placenta delivered manually in order to hasten the return of the patient to bed. After delivery of the placenta, 1 c.c. of pituitrin was given, the uterus contracted firmly, and there was no more bleeding. Patient was quickly returned to bed at 5:00 P.M. and given another 1,000 c.c. of saline and 5 per cent glucose.

By 8:00 P.M., one was able to feel a feeble pulse at the wrist, and the blood pressure registered 60/0. A continuous hyperdermoclysis of normal saline was continued through the night, and by 7:00 A.M., the next morning the pulse could be counted at 135 and blood pressure registered 105/70. The patient ran a temperature between 99° and 102° from the second to the seventh day, but otherwise made an uneventful recovery, and was up doing her work in three weeks.

# Society Transactions

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## BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF DECEMBER 7, 1934

The following papers were presented:

**Chorionepithelioma With a Long Latent Period.** Dr. David Feiner. (See page 840.) Discussed by Dr. S. A. Wolfe.

**The Pelvic Fascia.** Dr. Nathan P. Sears (by invitation). (See page 834.) Discussion opened by Dr. O. P. Humpstone.

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Dougal, Daniel: **Ovarian Conditions as Causes of Pelvic Pain**, Brit. M. J. 2: 621, 1934.

The author describes ovarian pain as one of the "bugbears" of medical practice. True ovarian pain is splanchnic and apparently of a low order; reflected superficial pain of ovarian origin only occurs when the parietal peritoneum is irritated by the ovary. Ovarian conditions producing pelvic pain may be grouped under four headings: functional, mechanical, inflammatory, and neoplastic.

In discussing the functional disturbances, pros and cons are given concerning the possible etiologic bearing of cirrhosis and sclerocystic disease of the ovary as well as of ovarian dysmenorrhea. In treating this group of disturbances, mention is made of excision of ovarian nerves in the hilum of the ovary as well as of organotherapy.

In discussing mechanical disturbances of the ovary, the author regards prolapse of the ovary generally beneath a retroverted uterus as most common and also mentions varicocele of the broad ligament and torsion of the ovarian pedicle.

Inflammatory disturbances of the ovary usually follow a salpingitis when the ovary becomes adherent to the neighboring structures. Pelvic peritonitis may be an associated causal factor of pelvic pain.

In conclusion, the author states that while neoplasms of the ovary are practically painless unless torsion, degeneration or infection occurs, endometrioma is an exception because by its adherence it causes stretching of the ovary from effused menstrual blood and also causes irritation of the nerves in the broad ligament and of the parietal peritoneum.

F. L. ADAIR AND I. C. UDESKY.



# American Journal of Obstetrics and Gynecology

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EDITORS: GEORGE W. KOSMAK, M.D., AND HUGO EHRENFEST, M.D.

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## Editorials

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### Present Status of Endocrinologic Diagnosis and Treatment

NO BRANCH of medicine during this century has made such enormous strides as endocrinology. This impetus was given by gynecologists and obstetricians including Fraenkel, Fellner, Oekinschitz, Herrmann, and Halban, in the years from 1903 to 1917. Surgeons, particularly Cushing, and also a gynecologist, Aschner, were among those who initiated the studies on the pituitary. The ever-increasing clan of endocrinology has enlisted assistance from all directions including internists whose accurate observations on various symptom complexes have been invaluable. Pathologists, physiologists, biochemists, and organochemists as well as physicists have performed important work in this field.

In consequence of this mass work, many dark and uncertain phases of medicine have been illuminated, but much still remains to be clarified.

The rapid advance has left the subject in the chaotic state of a new mining camp before law and order has been introduced. Wheat and chaff have not been separated. Innumerable reports of isolated observations are confusing even to the initiate, so that the average practitioner in despair frequently turns to the advertising literature and the detail man for information, which at least is positive, clear-cut, although often erroneous.

In trying to evaluate, particularly, the therapeutic weapons at our disposal, three types of results are apparent.

The first is clear-cut and unmistakable, such as the effects of thyroid preparations and insulin.

The second, remedies which are biologically assayable in the laboratory and give fairly concordant results when applied to the patient, such as the effect on the calcium metabolism produced by parathyroid extract or the relief of "shock" in Addison's disease obtained by *potent*

extracts of the adrenal cortex, and here the word of warning issued by Rogoff\* as to the lack of value of many of these preparations is pertinent.

The third includes the large number of preparations which exert assayable influence on laboratory animals but whose clinical effects either are unconvincing or allow of many interpretations.

This latter group is of particular interest to the gynecologist and obstetrician, as in it are included the prepituitary and prepituitary-like hormones, the estrogenic and corpus luteum hormones. On laboratory animals the bio-assay is convincing. On the human being the results are no more striking and concordant than in the days when patients were given desiccated ovarian and pituitary preparations, which increase in our knowledge has shown were devoid of any physiologic effect.

Of all the patients treated with this type of endocrine products, only two groups permit of any critical analysis: the sufferers from *dysmenorrhea* and the *menopause*. It is essential to exclude both amenorrheas and meno- and metrorrhagia from a critical and objective review, for, as is well known, return to normal function takes place in so many instances without detectable change and without any endocrine or other therapy, that observations based upon these groups must be thrown out of court. There are records available of many cases where primary amenorrhea, as well as excessive bleeding, extending over periods of many years and where long courses of "treatment" have proved ineffective, spontaneously recover.

Allowing for this possibility of error, one still might be convinced by sufficient statistical proof of carefully studied and large groups of patients, if the results of many observers were concordant. But they do not tally. It is striking and significant that usually those authorities who in years gone by obtained gratifying results with remedies, which we now know were biologically inert, are the ones who today again herald their therapeutic triumphs by the use of newer drugs. This need not imply bad faith but merely lack of critical judgment.

Even when dealing with such definite symptoms as dysmenorrhea, great caution must be exercised. Let us remember that the stem pessary, dilatation and discission of the cervix, the Dudley, Pozzi and Blair Bell operations, cauterization of the nasal spots, benzyl benzoate and other remedies, have been lauded, accepted, and discarded in turn. The same applies to the cure of menopause symptoms, where ovarian desiccates, ovarian residue, desiccated corpus luteum extracts, estrogenic hormone have been hailed as panaceas but have not stood the acid test of continued trial.

The causes which produce dysmenorrhea and the menopause syndrome are not understood. There is evidence to support the thesis that the symptoms may be due not to one but to several basic disturbances, to

\*Rogoff, J. M.: J. A. M. A. 103: 1764, 1934.

over- as well as to underproduction or possibly to failure of interaction of various hormones. The indecent haste with which certain clinicians inject into their docile patients the latest hormonal fraction, whether obtained from pregnancy urine, the ovarian follicle, the thymus, the middle lobe of the pituitary or the placenta, is revolting. The conclusions they draw are equally hasty and unreliable. Next month or year they will be off on another tangent with undiminished enthusiasm and optimism.

The prospect that eventually hormone therapy of gynecologic and obstetric functional disturbances will be put on a rational and effective basis is excellent. Such result will develop from well-selected, carefully controlled, and objectively studied series of cases; perhaps by trial and error, certainly not by machine gun type of endocrine drugging to which the profession is becoming addicted.

*Robert T. Frank.*

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### Certain Influences on Cancer Production

THE conflicting rôles of heredity and environment in the production of cancer have been in theory reconciled in a recent article by Lynch in the *Bulletin of the American Society for the Control of Cancer*. Her thesis is briefly that heredity may determine general susceptibility and even a predisposition to localization in certain organs, but that environmental factors will have a deciding influence on the final appearance of the growth in the available organ. Conversely, the effectiveness of an external agent to produce cancer is limited by a factor inherent in the constitution of the individual.

Many examples are found among the tumors of the female pelvis to illustrate these environmental and constitutional factors. Particularly in the glandular forms of carcinoma of the uterus and its appendages, evidences of constitutional and hence probably hereditary influences are important. Thus, there is the oft cited abnormality in onset of puberty and menstrual type and the relative infertility of women with certain types of adenocarcinoma of the uterus and ovary. Further evidence of a general predisposition is found in the common occurrence of multiple tumors, such as the coincidence of myoma and adenocarcinoma of the uterus and myoma with adenocarcinoma of the ovary. Spontaneous bilateral development of ovarian tumors and the appearance of multiple papillomas in independent locules of many ovarian cysts are further examples. The evidence of an at least "protective" effect of such an internal factor as the ovarian secretion is found in the atrophy of myomas and endometriosis after the normal or artificial menopause. Whether a

"causal" relationship exists, as recent studies have suggested, between certain pelvic tumors and dysfunctions of the ovary is not so well established.

The origin of the squamous type of cancer, that of the cervix and vagina in particular, appears more closely associated with environmental conditions, especially the chronic irritation accompanying laceration or infection. The occasional occurrence of cancer at the site of contact with a pessary is a less common, but striking, example of cancer from external sources. There is, furthermore, little tendency for these tumors to be multiple and locally acting forces appear therefore to play the predominant rôle.

After consideration of the specific functions of the various tissues of the pelvic organs, one is tempted to offer the hypothesis that the hormone controlled glandular tissues will yield tumors as a result of endogenous agents, possibly in the form of hereditary disturbances of function, while the squamous epithelium of the cervix and vagina will produce abnormal growth when its normal function, that of acting as a protective covering to the deeper tissues, is excited for a long period by chemical or mechanical irritants. There are, however, observations to upset such a clear distinction. Inflammatory factors are found in the adenomyosis of the uterine cornua and are suggested in certain cases of tubal and ovarian cancer and in the reported association of adenocarcinoma and tuberculosis of the endometrium. Furthermore, though chronic irritation may appear of paramount importance in cervical cancer, a constitutional factor is perhaps necessary to explain why one patient with a slightly diseased cervix will develop cancer while a hundred women will carry badly lacerated and infected cervixes for years without the development of any neoplastic complication. A fine example of a combination of constitutional and environmental factors is found in the cancer of the vulva which may develop as a result of a chronic inflammatory condition in a preexistent leucoplakia, which itself may have a constitutional basis.

The neoplasms of the pelvis are in many ways particularly favorable for research. They are common and are easily obtainable in large groups. Historical data on the reproductive and menstrual functions and the symptoms of chronic infection are more accurate than for most other systems of the body. Pelvic tumors are, furthermore, for the most part fairly accessible to the examining hand or eye. Finally, the factors producing normal growth and atrophy are rapidly becoming better known and are more readily studied for this region than for any other in the body. The pelvis is, therefore, a most promising field for further study and one from which much may be hoped toward the ultimate solution of the problem of neoplastic disease.

*Howard C. Taylor, Jr.*

# Department of Reviews and Abstracts

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CONDUCTED BY HUGO EHRENFEST, M.D.

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## Selected Abstracts

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### Pregnancy Complicated With Diseases of Pancreas and Kidney

Rosenloecher, K.: Changes in the Pancreas During Pregnancy in Women and in Animals, *Arch. f. Gynäk.* 151: 567, 1932.

The author made histologic studies of the pancreas of pregnant and nonpregnant animals and of women dying during or shortly after pregnancy. He finds a definite increase in the size and number of the isles of Langerhans. There is also an increase in zymogen granules. Changes in the pancreas are noted in the parenchyma as well as in the islands of Langerhans. Apparently the greatest increase in pancreatic activity occurs during the middle trimester of pregnancy and toward the end of pregnancy.

RALPH A. REIS.

Duncan, G. G., and Fetter, F.: The Effect of Pregnancy on the Insulin Requirement of the Diabetic, *Am. J. M. Sc.* 187: 347, 1934.

Exact control of diabetes throughout the course of pregnancy will prevent abnormal demands on the pancreas of the fetus. By adopting such a practice the insulin requirement increases in the first trimester, remains constant in the second, increases in the third and decreases suddenly after delivery. Pregnancy under ideal conditions and proper treatment does not permanently impair the diabetic's tolerance. Diabetes by itself is not a contraindication to pregnancy.

J. THORNWELL WITHERSPOON.

Eyding, A.: Diabetes and Pregnancy, *Zentralbl. f. Gynäk.* 57: 514, 1933.

Three women with diabetes during pregnancy, coming under the author's observation in one year, are reported. In 2 of them, pregnancy was allowed to go to term. In the third woman pregnancy was interrupted because she also had hypertension and excessive adiposity. In the 2 women who went to term, the sugar tolerance increased as pregnancy neared the end, but dropped again after the baby was born. The typical complications seen in pregnant diabetics, namely, acidosis, hydramnios and excessive skin depot fat in the babies, were all noted in the women who went to term. Pregnancy is rare in diabetics, but the author thinks that a higher conception ratio is possible with the use of insulin. The value of operative delivery is questionable.

WILLIAM F. MENGERT.

Liebmann, S.: The Course of Diabetes Complicating Pregnancy and Labor, *Monatsh. f. Geburtsh. u. Gynäk.* 91: 398, 1932.

Among 22,773 cases of pregnancy and miscarriage there were 12 women who had more or less severe, true diabetes (0.05 per cent), which expresses the infrequency of this ailment in pregnant women. Eight of these patients were seen before or at the beginning of the era of insulin. In only 4 cases was it thought advisable to interrupt the gestation. One patient died in spite of the therapeutic abortion. Most authors still favor interrupting the pregnancy in severe cases because of the seriousness of coma. Good results in diabetic pregnant women may be obtained by the use of a proper diet and insulin throughout gestation but when insulin is not administered until the patient is in coma, not much can be accomplished. It is generally believed that under proper management the life of a diabetic pregnant woman is not jeopardized and if proper precautions are taken labor and the puerperium are uncomplicated. However, extraneous circumstances may arise and lead to complications. Diabetic women should be delivered in a hospital. Pregnancy should be interrupted when there is a high degree of acidosis and especially when the ketonuria increases during pregnancy; when the sugar tolerance decreases and more and more insulin is necessary, and when any unlooked-for complications arise. In mild cases, when diet and insulin can maintain the proper sugar tolerance without much difficulty, the patient may safely nurse her baby.

J. P. GREENHILL.

Bix, H.: The Relationship Between Maternal Diabetes and Giant Children, *Med. Klin.* 29: 50, 1933.

Pregnancy in diabetic women is not common. If conception does take place the diabetes usually has an unfavorable effect on the fetus because abortions are frequent and children born at full term are weak and have a high death rate during the first few days of life. On the other hand, diabetic women not infrequently give birth to very large babies. The cause of this is considered to be the high blood sugar in the mother furthering the growth of the fetus. Bix investigated a series of 192 married diabetic women. Among this group 37 (19.4 per cent) had never been pregnant. The other 155 women had 608 children of which 63.3 per cent were of normal weight, 18.1 per cent weighed more than 4,000 gm., 7.7 per cent more than 4,500 gm. and 10.9 per cent 5,000 gm. or more. Hence more than 37 per cent of the children were overdeveloped. In an occasional case, a giant child was the first manifestation of a latent diabetes. Hence when a woman gives birth to an unusually large baby, a careful investigation should be undertaken to determine whether or not she has latent or active diabetes. Even if the findings are negative, the woman should be carefully observed for a long time afterward.

J. P. GREENHILL.

Theobald, G. W.: The Relationship of the Albuminuria of Pregnancy to Chronic Nephritis, *Lancet* 1: 626, 1933.

Bright's disease is causally associated with environment and heredity, but more intimately and predominantly with age. The following facts tend to prove that pregnancy and childbirth have relatively little causal association with chronic nephritis: (1) Mortality curves for women follow the same upward and downward trends as those for men; (2) mortality rates for Bright's disease are the lowest in rural districts in which those for albuminuria and convulsions are usually highest; (3) mortality among young widows is strikingly high; (4) there is very little difference in mortality rates for married and single women up to the age of 55.

The risks of marriage and childbirth are less than those of a spinster at any age after thirty years, while Bright's disease has a considerably higher mortality in single, than in married, women after fifty-five years. The author warns that chronic nephritis is too frequently charged to the so-called toxemias of pregnancy and implies that such views lead to an increase in the number of abortions and obscure the actual etiology of either "toxemia of pregnancy" or Bright's disease.

H. CLOSE HESSELTINE.

**Batisweller, J.:** The Connection Between Premature Separation of the Placenta and Renal Disease, *Arch. f. Gynäk.* 153: 536, 1933.

The author finds that renal disease of the type which may lead to anuria is frequently present in women in whom there is a premature separation of the placenta. This type of renal disease resembles interstitial nephritis with only slight degenerative changes. There is usually no edema and the blood chlorides are normal, but the rest—nitrogen and blood pressure are increased. Eclampsia rarely occurs. Chronic renal suppuration may be present or there may be marked edema of the interstitial portions of the kidneys.

The therapeutic problem remains unsolved. Decapsulation of the kidneys may be successful but is not in general use because of the seriousness of the procedure and because some failures have been reported. The author recommends the administration of large quantities of fluids (5 to 6 liters per day). These are given orally, rectally, subcutaneously and intravenously in order to keep the blood pressure high since maintenance of a high blood pressure is a protective mechanism against the development of anuria.

RALPH A. REIS.

**Kellar, R. J., and Arnott, W. M.:** Bilateral Cortical Necrosis of the Kidneys, *Edinburgh M. J.* 40: 101, 1933.

Bilateral cortical necrosis is an uncommon but dramatic complication of pregnancy. With its principal clinical feature of extreme anuria and its characteristic gross pathologic features it provides a peculiarly precise syndrome.

In 40 of the approximately 50 recorded cases, the condition was associated with pregnancy. It shows no tendency to select the primipara and most cases are found in the twenty-five to thirty-five age period. It usually supervenes during the fifth, sixth or seventh month of pregnancy. Previous pregnancies are usually normal. The course of the pregnancy up to the onset of the condition may be quite uneventful but more usually there are disturbances indicative of a degree of toxemia. These may be hyperemesis, headaches, edema, dimness of vision, etc.

Some of the cases have been associated with eclampsia or some other toxic manifestation, such as concealed accidental hemorrhage, but in the majority the patient is more likely to come under notice because of vaginal bleeding or some sign of impending delivery.

The one invariable clinical feature is anuria. This may be absolute or may be an extreme oliguria. It may be of short duration or it may endure for the astounding period of twenty to twenty-five days.

The closing stages are marked clinically by progressive exhaustion and there may be some terminal infection. The classical symptoms of uremia such as amaurosis, periods of unconsciousness, severe convulsions, etc., are usually absent. The blood pressure is usually normal. Edema is frequently present although it is not a prominent feature.

be actively treated or else the resultant cervicitis, even though the vulvovaginitis is cleared by hormonal therapy, will remain as a focus of infection from which the disease could persist.

Another unpleasant feature of this therapy is the technic of administering the hormone, the daily hypodermic injection. When the novelty of the treatment wears off, the daily visit to the clinic, by parent and patient, to be "stuck," becomes a very definite problem.

TABLE I

AGE	DURATION OF DISEASE	AMOUNT OF DISCHARGE	VAGINAL SMEAR AT ONSET	DURATION OF TREATMENT	DAILY DOSES	SMEARS AT END OF ONE MONTH	TWO MONTHS	THREE MONTHS	SMEAR AT END OF TREATMENT	LOCAL REACTIONS
9	Birth	Heavy	+	42 d	50 R.U.	+			+	0
6	9 mo.	Mod.	+	82 d	50 and 100 R.U.	+	+		+	Pain
10	9 yr.	Heavy	+	50 d	50 and 100 R.U.	+			+	0
2	2 wk.	Heavy	+	50 d	50 and 100 R.U.	+			+	0
4	1½ yr.	Mod.	+	42 d	50 R.U.	+			+	0
9	1 yr.	Heavy	+	92 d	50 and 100 R.U.	+	+	+	+	Pain
7	2 yr.	Heavy	+	66 d	50 and 100 R.U.	+	+		+	0
5	7 mo.	Mod.	+	54 d	50 R.U.	+			+	0
6	15 mo.	Heavy	+	68 d	50 and 100 R.U.	+	+		+	0
8	10 mo.	Heavy	+	50 d	50 R.U.	+			+	Pain

Occasionally enlargement of the breasts, hyperemia and hypertrophy of the vulva and uterine spotting occur. Such findings undoubtedly cause grave concern to the parents, no matter how beneficial the treatment.

The retail cost of the hormone, approximately one dollar per cubic centimeter, limits the private practice of this condition, especially when the course of treatment extends two to three months.

It is with great regret that we cannot substantiate Lewis' claims for this method of therapy. We do, however, anticipate other reports confirming the findings noted in this letter.

J. THORNWELL WITHERSPOON, M.A. (OXON) M.D.

Tulane University Medical School  
New Orleans, La.



Dear Doctor Kosmak:

In the article entitled "Harmful Effects of Certain Chemical Substances Upon the Uterus of the Rat," by Mr. Kiven and myself (this Journal, vol. 29, No. 4, April, 1935), I regret that I did not quote correctly a reference to an article which appeared in the *Journal of the American Medical Association* of June 11, 1932, page 2155. This is a report of the Bureau of Investigation. In reviewing this article I state that the Bureau has found reports of some 25 fatal cases resulting from the use of "Provocal." (This is the name under which Leunbach paste is sold abroad.) The fact of the matter is that in this report both Provocal and another paste (Interruptin) are discussed and the statement is made that "there have recently appeared in German literature reports of 25 deaths that have resulted from the use of these abortifacient pastes."

In justice to the manufacturers I would ask you to publish this correction.

Yours very truly,

(Signed) FRED E. D'AMOUR.

Denver, Colorado.

May 6, 1935.

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Hulpleu, Weatherby, and Culbertson: A Comparative Study of the Kelly Test and the Friedman Modification of the Zondek-Aschheim Test for Pregnancy, *J. Lab. & Clin. Med.* 20: 63, 1934.

The Kelly pregnancy test depends upon the fact that urine from pregnant women will cause the premature opening of the vaginal orifice of immature rats. The technic, slightly modified by these authors, consists in the intraperitoneal injection of 2.5 c.c. of urine, twice on successive days. The final examination of the rats is made at the end of ninety-six hours. The urine is rendered neutral to litmus, filtered and warmed approximately to body temperature before injection. Catheterized specimens are used in most instances.

In this series a total of 59 cases were studied. Friedman tests were also carried out from the same urine specimens. By checking with the subsequent histories of the patients there were 19 cases of pregnancy and 40 with no pregnancy. The Friedman test showed 20 positives and the Kelly test 21 positives. The error in the Friedman test was due to retention of part of the placenta after an abortion; the Kelly test showed this same error. The other error in the Kelly test occurred in the case of an ovarian cyst; the Friedman test on this case was negative.

The Friedman test depends upon the presence of an anterior pituitary hormone in pregnancy urine, while the Kelly test depends upon increased secretion of female sex hormone by the rat as a result of the stimulation of its ovaries by anterior pituitary hormone found in pregnancy urine. In certain pathologic conditions of nonpregnant women, sufficient female sex hormone may be excreted in the urine to produce a premature opening of the vaginal orifice in the rat, and thus give a false positive Kelly test as in the ovarian cyst case.

There were thirty-eight negative results from the Friedman test which were correct; one animal died. There were twenty-nine negative results from the Kelly test which were correct, and nine rats died. The earliest positive test was obtained one month after the last period, and another was positive approximately six weeks after the last period. The Kelly test has several advantages when compared with the Friedman test, viz: ease of handling animals, economy, and it is not necessary to kill or operate on the test animal. The disadvantages are: approximately double the time is required, certain pathologic conditions in which a large amount of female sex hormone is excreted in the urine may give false positive results, and the mortality rate among the rats is likely to be high as a result of intraperitoneal injections.

W. B. SERBIN.

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